

Insulin Glargine and Cancer—An Unsubstantiated Allegation

Satish K. Garg, M.D.,¹ Irl B. Hirsch, M.D.,² and Jay S. Skyler, M.D., M.A.C.P.³

To kill an error is as good a service, and sometimes even better than the establishing of a new truth or fact.

—Charles Darwin

IT HAS LONG BEEN KNOWN that both obesity^{1–4} and type 2 diabetes^{5–15} are associated with an increased risk of cancer. For type 2 diabetes, this has been particularly recognized with pancreatic cancer,^{6,12} colorectal cancer,^{8,11} and breast cancer.¹³ It has long been known that insulin can stimulate breast cancer growth in tissue culture.¹⁶ Many papers have examined the relationship between insulin and insulin-like growth factor (IGF) signaling in neoplasia and the possible effects of insulin in stimulating neoplasia via binding to the IGF-1 receptor.¹⁷ It is upon that background that recent events have erupted, bringing confusion to the situation.

On Friday, June 26, 2009, the EASD (European Association for the Study of Diabetes) released on its website (<http://webcast.easd.org/press/glargine/glargine.html>) and that of its journal *Diabetologia* (<http://www.diabetologia-journal.org/cancer.html>) a series of papers, an editorial, a press release, a video statement, and patient information, all concerning a “possible link between insulin glargine and cancer,” as the press release was titled, or “Lantus insulin: a possible link with cancer which requires further investigation,” as both websites heralded. This triggered a global panic among patients with diabetes and those who care for them, as insulin glargine (Lantus[®], sanofi-aventis, Paris, France) is the most widely prescribed insulin in the United States, accounting for 37.5% of all prescriptions. Position statements have been issued by multiple organizations, including the American Diabetes Association, the American Association of Clinical Endocrinologists, the Endocrine Society, and the International Diabetes Federation, in addition to the original EASD statement. As a group, these statements asserted that there was only an unproven link between insulin glargine and cancer and advised patients to consult their physician before changing insulin. They urged further research. Unfortunately, the statements generally were unhelpful to physicians needing to make patient care decisions. This situation has prompted the authors to write this editorial assessing the papers, the data, and the circumstances and recommending a course of action.

First, we should examine how it came to be that there were multiple papers appearing on-line addressing the relationship

of insulin glargine and cancer. The editorial explains this and hypothesizes how insulin in general (and insulin glargine in particular) could increase cancer risk, specifically through an increase in binding to the IGF-1 receptor.¹⁸

The original article submitted was an examination of a German claims database¹⁹ carried out by The Institute for Quality and Efficiency in Health Care (IQWiG), a German group that makes healthcare recommendations and that previously took the position that insulin analogs offer no benefit over conventional human insulin.²⁰ This raises questions as to the motivation of IQWiG in conducting the reported analyses. So, what did they find? First, it should be appreciated that the mean age of subjects in the analysis was 69.5 years. Because of the way the information was collected, there is no information available on their duration of diabetes, their degree of diabetes control (e.g., glycosylated hemoglobin), or their body mass index—all important information. Also, the types of malignancy found in these patients were not reported.

Furthermore, in the German study,¹⁹ for all cancers, when insulin glargine is compared to human insulin the unadjusted hazard ratio (HR) is 0.85 (95% confidence interval [CI], 0.79–0.93), indicating a significant 15% decrease in cancer with insulin glargine. A similar outcome is seen when adjusted for age and gender, namely, an HR of 0.86 (95% CI, 0.79–0.94). And, a similar finding was seen for all-cause mortality: an HR of 0.68 (95% CI, 0.65, 0.72). All of these HRs are statistically significant. An increased cancer risk for insulin glargine is only evident if there is further adjustment for dose of insulin. However, for that to be a valid adjustment, the subjects should have been classified by dose group when enrolled; instead, the investigators calculated an average dose over the duration of exposure. Moreover, any subject who changed insulin type during the study was removed from the analysis, resulting in a large number of exclusions. Further, there was a large imbalance in the proportion of subjects in the highest dose category—for glargine, this group was 13.5% of all subjects using glargine, whereas for human insulin it was 46.0% of subjects. Thus, in the highest dose group (>40 units daily), there were 103 events among glargine users and 2,075

¹Barbara Davis Center for Childhood Diabetes, Aurora, Colorado.

²University of Washington Medical Center–Roosevelt, Seattle, Washington.

³Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, Florida.

Dr. Garg is Editor-in-Chief and Dr. Skyler is Associate Editor of *Diabetes Technology and Therapeutics*.

among users of human insulin. Given all this, it is our view that the dose relationship analysis is flawed and thus cannot be interpreted. Rather, the overall analysis not adjusting for dose, if anything, indicates that there is a decrease in both cancer risk and all-cause mortality when insulin glargine is compared to human insulin. Our overall thought is that the three of the six referees who initially rejected this article were correct that there was not enough evidence to publish this article.

As the Editors explained,¹⁸ after receiving mixed reviews about the German study, they then requested that three other groups examine their databases to see if they could confirm the German findings. The three groups were from Sweden, Scotland, and the United Kingdom. In contrast to the flawed analysis in the German study, these three studies do follow rules of proper data analysis.

In the Swedish study,²¹ the investigators examined data from a number of databases and joined them for analysis. The databases included the Prescribed Drug Register, the Swedish National Diabetes Register, the Cancer Register, and the Causes of Death Register, targeting specific persons. When comparing users of insulin glargine to users of other insulins, they found that the relative risk (RR) for all cancers was 1.07 (95% CI, 0.91–1.27), indicating that there was no difference in risk. However, in a secondary analysis, when they examined the risk for breast cancer, they made some surprising observations. For users of insulin glargine alone (no other insulins used), there was an increased risk for breast cancer, namely, an RR of 1.99 (95% CI, 1.31–3.03); yet, for users of insulin glargine in combination with another insulin, there was no increase in risk (RR 1.10 [95% CI, 0.77–1.56]). Moreover, in spite of the apparent increased risk of breast cancer in users of insulin glargine alone, among women (who presumably have most or all of the breast cancers) who were users of insulin glargine alone, for all-cause mortality there was a decrease in risk of 17%, with an RR of 0.83 (95% CI, 0.71–0.96). This decrease in all-cause mortality was also observed among women who used insulin glargine in combination with another insulin, with an RR of 0.87 (95% CI, 0.77–0.97). The authors appeared confused about their findings and state “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.” They further state “we have no evidence of whether the difference in incidence rate for breast cancer among users of insulin glargine monotherapy, 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 monotherapy group. Any suggestion of an explanation would be pure speculation.” Most importantly, in our view, the decrease in all-cause mortality suggests that the apparent increased rate of breast cancer did not result in death.

The Scottish Diabetes Research Network (SDRN) Epidemiology Group also examined its diabetes database, to obtain data on the relationship between insulin glargine use and cancer incidence.²² Overall, they found that for all cancers, when all insulin glargine users are considered, there was not an increase in risk, with the HR being 1.02 (95% CI, 0.77–1.36). Moreover, also for breast cancer, when all insulin glargine users are considered, there was not an increase in risk, with

the HR being 1.49 (95% CI, 0.79–2.83). Taking a cue from the Swedish study, in a secondary analysis, they then calculated the rate of breast cancer among users of insulin glargine alone, in comparison to users of insulins other than insulin glargine, and in this case found an HR of 3.39 (95% CI, 1.46–7.85), but this was based on just six events in the glargine-only group. They also did find an increased overall cancer risk in this subgroup (HR 1.55 [95% CI, 1.01–2.37]). The authors conclude that “observational analysis of drug effects is not a substitute for randomized trials because, fundamentally, one can never completely rule out allocation bias except by random allocation. Observational analyses can raise hypotheses about harm and in many cases they can provide reassurance about harm. Whilst our data do not provide complete reassurance about cancer rates and insulin glargine use, neither do they point to unequivocal evidence of harm.” The authors conclude that the subgroup effects most likely reflect allocation bias (i.e., those less healthy in many ways being treated with insulin glargine on its own).

The third database to be examined at the request of the Editors was The Health Information Network (THIN), which includes data from approximately 300 general practices in the United Kingdom (UK).²³ They found that metformin monotherapy carried the lowest risk of cancer, whereas in comparison to metformin, there was an increased cancer risk either with insulin secretagogues or with insulin. The adjusted HR for cancer risk for all insulin regimens was 1.42 (95% CI, 1.27–1.60). For those on basal human insulin alone versus insulin glargine alone, there was no difference in HR (1.24 [95% CI, 0.90–1.70]). For breast cancer, when comparing insulin glargine with other insulins, there was no increase in risk (HR 0.86 [95% CI, 0.42–1.75]). However, compared with metformin, insulin therapy did increase the risk of colorectal cancer and pancreatic cancer but did not influence the risk of breast or prostate cancer. Thus, in the THIN analysis, use of insulin analogs (including insulin glargine) was not associated with increased cancer risk as compared with human insulin.

On the Web, there also was a Letter to the Editor²⁴ reporting a summary of neoplasms in a small series of 1,017 subjects followed for over 4 years in a randomized controlled trial comparing insulin glargine with NPH insulin. In this study, for all neoplasms, the risk ratio for insulin glargine was 0.90 (95% CI, 0.64–1.26); for neoplasms listed as serious adverse events, it was 0.63 (95% CI, 0.36–1.09); and for breast cancer it was 0.59 (95% CI, 0.14–2.44), but there were only eight breast cancers. The advantage of this study is that it was a randomized trial, but the number of subjects was very small.

In summary, if we discard the supposed dose effect, which we have explained is not valid, none of the studies shows a relationship between insulin glargine and cancer. What these studies did show is: (1) the German study¹⁹ found that there is a decrease in both cancer risk and all-cause mortality when insulin glargine is compared to human insulin; (2) the Swedish study²¹ found no increase in overall cancer risk with insulin glargine, but for breast cancer an increased risk with use of insulin glargine alone, but not in combination with other insulins, and with a decrease in all-cause mortality; (3) the Scottish study²² found no increase in overall cancer risk with insulin glargine and uninterpretable data with regard to breast cancer; (4) the UK THIN study²³ found no increase in overall cancer risk and no increase in breast cancer risk with

insulin glargine but did find an increase in risk with insulin and insulin secretagogues versus metformin; and (5) the small randomized study²⁴ found no increase in cancer risk. This is in stark contrast to news headlines and reports that “insulin glargine (Lantus) increases cancer risk.”

The best way to establish or refute whether there is a relationship between insulin glargine and cancer would be through a prospective randomized controlled clinical trial. It is highly unlikely that such a trial will be conducted for this purpose. However, there is a large randomized trial that has been under way since 2003, the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) Trial.²⁵ ORIGIN has randomized 12,612 subjects, all of whom have already been followed for at least 3.5 years. This study evaluates early insulin use (with insulin glargine) in comparison to standard diabetes care. Examination of the frequency of cancer in ORIGIN may help resolve the question definitively if in the insulin glargine group there is a similar (or decreased) rate of cancer in comparison to the control group. However, if there is an increased rate of cancer in the insulin glargine group, it will be impossible to distinguish whether that increase is due to insulin use or insulin glargine use. Moreover, given the observation that metformin use may result in decreased cancer risk,^{23,26,27} the use of metformin, principally in the standard therapy group, may complicate analysis and make interpretation difficult. Nevertheless, we hope that the ORIGIN investigators will soon review the available data in regard to this important question.

Although patient safety is of paramount importance in the treatment of any disease, we do not think there is any reason to sensationalize unproven risks of a treatment, which might unwarrantedly deter patients from its use, as in the case of insulin glargine discussed here. All treatments carry some risk. Yet, risk must always be balanced with benefit. The benefits of good glycemic control in patients with diabetes are clearly established, particularly with regard to acute complications, microvascular complications, and neuropathy. Insulin glargine has proved to be an effective agent in helping achieve glycemic control while minimizing hypoglycemia. Our view is that insulin glargine should continue to be used, and certainly should not be discontinued on the basis of unsubstantiated allegations.

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Address correspondence to:

Satish K. Garg, M.D.

Professor of Medicine & Pediatrics

University of Colorado at Denver

1775 Aurora Court, A-140

Aurora, CO 80045

E-mail: Satish.Garg@ucdenver.edu