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Innocent Until Proven Guilty: Lantus® (Insulin Glargine)

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Recently within the past few months, four European observational studies have alarmed the healthcare community with information regarding a possible link between insulin glargine (Lantus®) use and cancer. In light of these findings, it is important to keep in mind that type 2 diabetes, obesity, and insulin resistance are also linked to cancer.¹ According to the CDC's National Diabetes Fact Sheet, 14% of American adults diagnosed with type 1 or type 2 diabetes are on insulin only, while 13% take insulin plus an oral medication.² In diabetic patients, the relative risk of colorectal cancer compared to non-diabetic patients has been found to be 1.30 (95% CI 1.2-1.4), while for bladder cancer the relative risk was found to be 1.24 (95% CI 1.08-1.42), and the hazard ratio for breast cancer was found to be 1.20 (95% CI 1.12-1.28).³ Interestingly, cancers of the colon, breast, and pancreas may increase levels of endogenous insulin in the non-diabetic population, which emphasizes the existence of a possible relationship between insulin and cancer.¹

This relationship may be based on insulin's activity as a growth factor in the body, and possibly as a growth factor for several epithelial tumors.¹ There is also a possibility that hyperinsulinemia increases the availability of insulin-like growth factor-1 (IGF-1), another tumor growth factor, which may further support a link between insulin and cancer.¹ It is hypothesized that insulin glargine may itself work similarly to IGF-1.⁶ Therefore, the question becomes, are all insulins equally guilty of leading to cancer? The answer based on these studies is no. Insulin analogues are suspected to be more to blame than human insulin. The growth of human mammary epithelial cells (HMEC) stimulated by insulin analogues corresponds with the analogue's ability to bind to the IGF-1 receptor, while mitotic activity is dependent on prolonged interaction with the receptor.¹ Alterations of the human insulin molecule in the development of faster- or longer-acting insulin analogues were found to speed up DNA synthesis and cell division in vitro, especially of HMECs.¹ In relation to human insulin, insulin glargine has been found to have a six- to eightfold stronger binding affinity and mitogenicity; this gives more reason to suspect insulin glargine of being guilty of leading to cancer.¹

The German insurance study was the pioneer of the four studies. This study compared the rates of diagnosis of malignant tumors in approximately 130,000 patients on human insulin, insulin lispro, insulin aspart, and insulin glargine over a time period of 1.63 years (See Table 1 below).^{1,3} It identified a dose-dependent relationship between insulin, regardless of the type, and the incidence of cancer.¹ When compared to human insulin, insulin glargine was found to have a higher dose-dependent risk for cancer (HR 1.09, $p < 0.0001$

at 10 units) than the other analogues.³ The crude incidence rates per 100 patient-years for malignant neoplasms varied based on the type of insulin used, and were found to be 2.50 in patients on human insulin, 2.16 in aspart-treated patients, 2.13 in those treated with lispro, and 2.14 in glargine-treated patients.³ However, insulin glargine was found to have a higher risk of malignant neoplasms when adjustments were made to consider patient characteristics and the insulin dosage.³ This study also found the mortality rates were higher (14.79 vs 9.17 per 100 patient-years) in high-dose glargine-treated patients (> 40 IU) than in patients on equivalent human insulin doses.³ The authors of this study concluded that the study results offer more substance to claims of the mitogenic and tumor growth-promoting actions of glargine.³

After the results of the German Insurance Study were known additional European studies were conducted to verify these findings, one of which was conducted in Sweden.⁶ The incidence rates of breast cancer, gastrointestinal cancer, prostate cancer and any type of malignancy linked to the use of insulin glargine and other types of insulin were determined by analysis of data from Sweden's Prescribed Drug Register and Cancer Register.⁶ Precancerous lesions were also evaluated, as well as in situ cancers as secondary outcomes. Incidence rates for any type of malignancy, gastrointestinal cancer, and prostate cancer were similar across treatment groups. This was not the case for breast cancer. Insulin glargine doubled the risk in women compared to other types of insulin (unadjusted RR 1.91; 95% CI 1.25-2.89)(adjusted for age RR 1.99; 95% CI 1.31-3.03). When insulin glargine was combined with other types of insulin, the breast cancer risks were slightly lower [unadjusted RR 0.92 (0.66-1.29), adjusted for age and sex RR 1.10 (0.77-1.56), and adjusted for age, BMI, smoking, age of diabetes onset, cardiovascular disease, and age of birth of first child RR 1.17 (0.81-1.68)].⁶ It is not clear why the combination of insulin glargine with other insulins was associated with a lower cancer risk, but some notable differences are that this group had a lower average age and had more type 1 diabetics than the other group. The adjusted relative risk for breast cancer due to any insulin glargine use was found to be 1.40 (1.04-1.89).⁶ This study establishes a high risk of breast cancer associated with insulin glargine use, but the authors acknowledged the need for other studies to be conducted to further evaluate this issue.⁶

The controversy of insulin glargine's ability to cause cancer is complicated by the results of the study conducted by the Scottish Diabetes Research Network Epidemiology Group. This study set out to determine if patients with diabetes using insulin glargine

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have a greater risk of cancer compared to other types of insulin. It must be noted that of the 36,254 subjects only 3,959 of them were on any insulin glargine, while a smaller portion (447/36,254) of the study population was on insulin glargine only. No overall difference was seen in all cancer rates among those patients on or not on insulin glargine (HR 1.02, 95% CI 0.77-1.36) (See Table 1 for more results). When examined overall, any insulin glargine use was not associated with an increased risk of breast cancer (HR 1.49, 95% CI 0.79-2.83, $p=0.2$). However, users of insulin glargine only did have a significantly higher rate of breast cancer compared to non-glargine users in the fixed cohort.⁵ The level of glycemic control in each group varied significantly with the hemoglobin A1c (HbA1c) being 8.6% in the non-glargine group, 8.9% in the non-glargine plus glargine group, and 9.4% in the glargine only group. Since the glycemic control in the glargine only group was worse than the other groups it may be appropriate to consider this as a possible contributing factor to differences found in cancer rates between the groups. Unlike the previous studies, the authors of this study concluded that insulin glargine use does not result in an increased cancer risk over a four year time span, and that any differences that exist in their results are due to allocation bias. It was also concluded that duration of exposure to insulin glargine therapy was not positively associated with cancer rates.⁵

The United Kingdom study which looked at patients participating in The Health Information Network (THIN) failed to show an association between insulin glargine use and cancer.⁴ It investigated the relative frequency at which cancer was diagnosed in Type 2 diabetics receiving various treatment regimens, including insulins.⁴ In comparison to metformin monotherapy, the hazard ratios of sulfonylurea monotherapy, oral combination therapy, and insulin-based regimens for the combined risk of progression to breast or colorectal or prostate cancer were 1.62 (95% CI 1.30-2.01), 1.07 (95% CI 0.87-1.31), and 1.55 (95% CI 1.27-1.89), respectively.⁴ The statistically significant findings for insulin treatment compared to metformin monotherapy were a hazard ratio of 1.69 (95% CI 1.23-2.33) for colorectal cancer, and a hazard ratio of 4.63 (95% CI 2.64-8.10) for pancreatic cancer.⁴ Interestingly, metformin was found in this study to have a protective effect against cancer (HR in insulin-treated patients 0.54, 95% CI 0.43-0.66), more specifically against colon and pancreatic cancer, as either monotherapy or combination therapy with a sulfonylurea or insulin.⁴ The adjusted risk for solid tumor progression in untreated diabetic patients was the same as that seen with metformin (HR 0.90, 95% CI 0.79-1.03).⁴ No difference was found in regards to progression to breast cancer when insulin glargine was compared to all of the other insulins (HR 0.86, 95% CI 0.42-1.75).⁴ It was concluded that the results of this study failed to show greater risk of cancer progression associated with insulin glargine and other insulin analogues, but the need for more detailed studies to further evaluate insulin safety was acknowledged.⁴

Several factors must be considered when interpreting and evaluating the results of these European studies. Keep in mind that these studies only observed subjects for a relatively short time period of exposure to various medications; therefore, the findings might not accurately represent cancer development secondary to insulin use since cancers develop over a longer time period. Another consideration to be made is that all of these studies were retrospective in nature; therefore they are not as powerful as prospective studies. In addition, the subjects of these studies are not representative of

the El Paso community, so applicability to our patient population is limited.

Although the findings of these studies may result in a desire to stop insulin glargine use in fear of cancer development, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have both released statements in discouraging the discontinuation of current insulin regimens until more conclusive information is available. The differentiation between insulin as a cause of cancer versus insulin as an accelerator of the progression of a pre-existing cancer must be made. As previously mentioned, cancers of the colon, breast, and pancreas may elevate levels of endogenous insulin in the non-diabetic population leading to conclusions that there may be a possible link between insulin (not just glargine) and cancer. The results of each study offer different perspectives on the potential relationship between insulin glargine and cancer. Prospective, randomized studies looking at the incidence of cancer in glargine vs non-glargine treated patients would be ideal; however, they would clearly be unethical to conduct since there has been evidence showing possible harm secondary to glargine use. Until more information becomes available, insulin therapy should be continued in patients at low risk for developing cancer, such as those without a personal history or family history of cancer. If a provider is concerned with using glargine, an insulin regimen based on regular insulin would be an option. Before black listing glargine, keep in mind that the diabetic patient population is already at risk for cancer due to risk factors like type 2 diabetes, obesity, and insulin resistance. Glargine should be considered innocent until it is proven to be guilty with more concrete evidence.

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Table 1: Comparison of European Studies

	German Insurance ^{3,1}	Sweden ^{6,1}	Scotland ^{5,1}	UK GP Database ^{4,1}
Study Design/Methods	<ul style="list-style-type: none"> Cohort study Purpose: investigate risk of neoplasms & mortality in diabetics treated for 1st time with human insulin or 1 of 3 insulin analogues (aspart, lispro, glargine) 	<ul style="list-style-type: none"> Population-based follow-up study Fixed-cohort analysis Purpose: to investigate the incidence rates of breast cancer, GI cancer, prostate cancer, and any type of malignancy associated with the use of insulin glargine vs other types of insulins 	<ul style="list-style-type: none"> Retrospective, cohort study Purpose: to examine whether patients with diabetes in Scotland using insulin glargine have a greater cancer risk than patients on other types of insulin 3 different analyses: fixed cohort, incident insulin cohort, exposure analysis 	<ul style="list-style-type: none"> Retrospective cohort study Purpose: to examine the relative frequency of cancer diagnosis in patients receiving different therapies for type 2 DM Divided into 4 groups: monotherapy with MTF or SU, combined therapy (MTF + SU), or insulin (further divided into insulin glargine, LA human insulin, BP analogue, and human BP insulin)
Outcomes	Primary: diagnosis of malignant neoplasm Secondary: all-cause mortality	5 malignancy outcomes (all malignant tumors, all malignant tumors + in situ tumors, breast cancer (women), prostate cancer, GI cancer)	Overall cancer incidence, and the frequency with which cancer of the breast, colon, prostate, and pancreas were diagnosed	Progression to any solid tumor or cancer of breast, colon, pancreas or prostate
N	127,031	114,841	36,254	62,809
Duration	avg. 1.63 years	# of person-years varied among the 5 malignancy outcomes	4 years	Total follow-up time: 152,065 person-years
Results	<ul style="list-style-type: none"> (+) association between cancer incidence and insulin dose for all insulin types adjusting for dose showed a dose-dependent ↑ in cancer risk for glargine vs human insulin (p<0.0001) 	<ul style="list-style-type: none"> women using insulin glargine alone had ↑ incidence rate of breast cancer; RR 1.91 (95% CI: 1.25-2.89) when not adjusted 95% CI for malignancy outcomes other than breast cancer were not significant for both adjusted and unadjusted numbers unadjusted incidence rate ratios for users of insulin glargine in combo with other insulins vs users of insulin other than glargine resulted in significant relative risk ↓ for all malignancy outcomes except breast cancer 	<ul style="list-style-type: none"> any insulin glargine use (n=3,959) had same incidence rate for all cancers as those not receiving insulin glargine (HR 1.02, 95% CI 0.77-1.36, p=0.9 in fixed cohort) insulin glargine alone (n=447) had significantly ↑ incidence of all cancers than those using other insulins only (n=32,295) [HR 1.55, 95% CI 1.01-2.37, p=0.045 in fixed cohort] insulin glargine + other insulins (n=3,512) had slightly ↓ incidence of all cancers in fixed cohort no significant ↑ in breast cancer rates with glargine overall (HR 1.49, 95% CI 0.79-2.83), however insulin glargine only users had a ? rate than those using non-glargine insulin only (HR 3.39, 95% CI 1.46-7.85, p=0.004 in fixed cohort) 	<ul style="list-style-type: none"> MTF monotherapy had lowest risk of cancer Adjusted HR was 1.08 (95% CI: 0.96-1.21) for MTF + SU, 1.36 (95% CI 1.19-1.54) for SU monotherapy, & 1.42 (95% CI 1.27-1.60) for insulin regimens Adding MTF to insulin ↓ progression to cancer (HR 0.54, 95% CI 0.43-0.66) Insulin vs MTF ↑ risk of colorectal (HR 1.69, 95% CI 1.23-2.33) or pancreatic cancer (HR 4.63, 95% CI 2.64-8.10)
Conclusions	Safety concerns exist based on mitogenic properties of glargine in diabetics	No definitive conclusions can be made regarding the possible causal relationship between insulin glargine use and occurrence of malignancies	Insulin glargine was not associated with ↑ risk of all cancers or site-specific cancers in Scotland	<ul style="list-style-type: none"> Patients on insulin or insulin secretagogues developed solid cancers more often than those on MTF insulin analogues did not show an ↑ cancer risk compared with human insulin would be premature to assume a causal relationship between insulin therapy and cancer
Limitations	<ul style="list-style-type: none"> Mean daily dose of glargine was much lower than for human insulin because combo therapy (insulin analogues + human insulin) patients were excluded Did not break down findings according to nature of tumor 	<ul style="list-style-type: none"> Possibilities for examining validity are limited Duration of insulin therapy and exposure to other insulins prior to 2005 could not be considered Could not examine dose-response relationship Lack data on potential confounding variables 	<ul style="list-style-type: none"> The excess cases of all cancers & breast cancer in the subgroup of insulin glargine only users are more likely a reflection of allocation bias no data available on drug dose short follow-up time for evaluating cancer effects 	<ul style="list-style-type: none"> Insufficient numbers to perform separate analyses for diabetes-related tumors, or for insulin detemir influence of insulin dose or duration of treatment could not be examined may have been under-reporting of cancer
Key Points	Established a dose-dependent relationship between insulin and cancer	Breast cancer risk found in insulin glargine only users	Also found more cancers (including breast) were diagnosed in patients on insulin glargine alone, but attributed to allocation bias	MTF was found to have a protective effect against cancer

*MTF = metformin, SU= sulfonylurea, LA=long-acting, BP = biphasic

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