Case 4: Concerns about Cancer Risk

- 58-year-old obese postmenopausal woman
- Long-standing type 2 diabetes
- Family history of both metabolic syndrome and breast cancer
- Currently inadequate control with premix insulin
- Considering changing to a basal-bolus insulin regimen with insulin glargine, but concerned about cancer risk with this strategy

Development of Insulin Analogs

<table>
<thead>
<tr>
<th>Sequences of Various Insulins (Natural and Analogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-Chain Position</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Human</td>
</tr>
<tr>
<td>Bovine</td>
</tr>
<tr>
<td>Porcine (also dog)</td>
</tr>
<tr>
<td>Aspart</td>
</tr>
<tr>
<td>Glulisine</td>
</tr>
<tr>
<td>Lispro</td>
</tr>
<tr>
<td>Detemir</td>
</tr>
<tr>
<td>Glargine</td>
</tr>
<tr>
<td>B10Asp</td>
</tr>
</tbody>
</table>
Mitogenic Potential of Insulin Analogs

Insulin B10Asp was the first of the insulin analogs developed. It has higher affinity for the insulin and IGF-1 receptors than native insulin, and higher mitogenicity in vitro.

<table>
<thead>
<tr>
<th>Mammary Tumors</th>
<th>Saline (UI/kg/day)</th>
<th>Human 200</th>
<th>B10Asp 12.5</th>
<th>B10Asp 50</th>
<th>B10Asp 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>0</td>
<td>0</td>
<td>11%</td>
<td>0</td>
<td>44%</td>
</tr>
<tr>
<td>Malignant</td>
<td>0</td>
<td>0</td>
<td>11%</td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>

Female rats were injected for one year with saline or insulin as indicated. A dose-dependent increase in incidence of mammary tumors was found on necropsy. No other neoplastic lesions were found.


Mitogenic Potential of Insulin Analogs

<table>
<thead>
<tr>
<th>Analog</th>
<th>Insulin Receptor Affinity (%)</th>
<th>Insulin Receptor Off-Rate (%)</th>
<th>Metabolic Potency (Lipogenesis) (%)</th>
<th>IGF-1 Receptor Affinity (%)</th>
<th>Mitogenic Potency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>B10Asp</td>
<td>205 ± 20</td>
<td>14 ± 1</td>
<td>207 ± 14</td>
<td>587 ± 50</td>
<td>975 ± 113</td>
</tr>
<tr>
<td>Aspart</td>
<td>82 ± 6</td>
<td>81 ± 8</td>
<td>101 ± 2</td>
<td>81 ± 9</td>
<td>55 ± 22</td>
</tr>
<tr>
<td>Lispro</td>
<td>84 ± 6</td>
<td>100 ± 11</td>
<td>82 ± 3</td>
<td>106 ± 16</td>
<td>66 ± 19</td>
</tr>
<tr>
<td>Glargine</td>
<td>86 ± 3</td>
<td>152 ± 13</td>
<td>60 ± 3</td>
<td>641 ± 91</td>
<td>783 ± 112</td>
</tr>
<tr>
<td>A21Gly</td>
<td>78 ± 10</td>
<td>162 ± 11</td>
<td>88 ± 3</td>
<td>42 ± 11</td>
<td>34 ± 12</td>
</tr>
<tr>
<td>B31B32dAsp</td>
<td>120 ± 4</td>
<td>75 ± 8</td>
<td>75 ± 5</td>
<td>204 ± 202</td>
<td>2180 ± 390</td>
</tr>
</tbody>
</table>


Concern About Insulin Glargine and Cancer...

Hemkens and colleagues utilized a large German insurance dataset to compare the rate of diagnosis of malignant tumors in patients treated with human insulin versus the insulin analogs aspart, lispro, and glargine. Those treated with multiple types of insulin were excluded.

Included 127,031 individuals (39% of all those using insulin):
95,804 (75.4%) exclusively on human insulin
23,855 (18.8%) insulin glargine alone
4,103 (3.2%) insulin aspart alone
3,269 (2.6%) insulin lispro alone


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The German Study (continued)

- First-time insulin users, no evidence of malignancy for prior 3 years
- Type of diabetes (1 or 2) and weight were not specified in the registry
- Primary outcome was malignancy of any type; secondary outcome was all-cause mortality
- Mean follow-up was 1.63 years for malignancy (maximum 4.41) and 1.67 years for mortality (maximum 4.41)
- Median age about 67 years


HRs for Malignant Neoplasms Referenced to Human Insulin

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Aspart</th>
<th>Lispro</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 U</td>
<td>0.98 (0.73–1.03)</td>
<td>0.85 (0.72–1.01)</td>
<td>0.85 (0.73–0.93)</td>
</tr>
<tr>
<td>Final Model</td>
<td>P=0.30</td>
<td>P=0.96</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>10 U</td>
<td>1.00 (0.82–1.21)</td>
<td>0.99 (0.82–1.19)</td>
<td>1.09 (1.00–1.19)</td>
</tr>
<tr>
<td>30 U</td>
<td>1.02 (0.85–1.22)</td>
<td>0.98 (0.83–1.16)</td>
<td>1.19 (1.10–1.30)</td>
</tr>
<tr>
<td>50 U</td>
<td>1.04 (0.87–1.24)</td>
<td>0.98 (0.83–1.16)</td>
<td>1.31 (1.20–1.42)</td>
</tr>
</tbody>
</table>


Conclusions/interpretation: Considering the overall relationship between insulin dose and cancer, and the lower dose with glargine, the cancer incidence with glargine was higher than expected compared with human insulin. Our results based on observational data support safety concerns surrounding the mitogenic properties of glargine in diabetic patients. Prospective long-term studies are needed to further evaluate the safety of insulin analogs, especially glargine.

Metabolism of Insulin Glargine

After subcutaneous injection, insulin glargine is metabolized by sequential cleavage at the carboxy terminus of the B chain, yielding products including A21Gly and A21Gly-des-30B-Thr insulins.

On average about 50% of insulin recovered from fat from the site of injection is cleavage products. Similar degradation processes have been observed in human sera.

A21Gly insulin has relatively low mitogenic potency.

Mitogenic Potential of Insulin Analogs

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<td>975 ± 173</td>
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<tr>
<td>Aspart</td>
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<td>101 ± 2</td>
<td>81 ± 5</td>
<td>56 ± 22</td>
</tr>
<tr>
<td>Lispro</td>
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<td>82 ± 3</td>
<td>156 ± 16</td>
<td>66 ± 10</td>
</tr>
<tr>
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<td>783 ± 132</td>
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<td>75 ± 5</td>
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Limitations of Observational Studies

- Large potential for bias
- The clinical decisions that determine each patient’s treatment are not random
- Difficult to adjust for confounders
- Residual selection bias may distort any true differences (or lack thereof)
- Issues of reverse causality
- Multiple hypothesis-testing may produce spurious results
### RCT Post-Hoc Analysis

- Original study designed to assess ocular complications of diabetes with insulin glargine compared to NPH insulin (no difference seen)
- 1017 patients randomized and treated: 514 insulin glargine, 503 NPH insulin
- Cumulative exposure was greater than 4 years
- Baseline demographics between the two groups were similar
- No difference in number of neoplasms between the two groups (57 or 11.1% for insulin glargine and 62 or 12.3% for NPH insulin)


### RCT ORIGIN Trial

- Insulin glargine versus placebo in patients with impaired fasting glucose or newly diagnosed type 2 diabetes
- 12,578 people have been randomized and will be followed for 6-7 years
- The study is due to end at end of 2011

Interim Safety Analysis:
"In light of the questions raised by the recent publication, this committee of experts has recently reviewed data related to cancers in both treatment groups and has concluded that there is no cause for concern and no reason to alter the design of the study for safety reasons."


### Obesity and Excess Cancer Risk

**Excess cancer risk for BMI increase of 5 kg/m²**

- **Men:**
  - Esophageal adenocarcinoma ~52%
  - Thyroid ~33%
  - Colon ~24%
  - Kidney ~24%
- **Women:**
  - Endometrium ~59%
  - Gallbladder ~59%
  - Esophageal adenocarcinoma ~51%
  - Kidney ~34%

Diabetes and Excess Cancer Risk

- Type 2 diabetes, significant excess cancer risk:
  - Breast ~20%
  - Colorectal ~30%
  - Endometrium ~110%
  - Liver ~150%
  - Bladder ~24%

- Type 1 diabetes, modest excess cancer risk:
  - Stomach
  - Cervix
  - Endometrium

Diabetes and Cancer, Shared Risk Factors

- Aging
- Obesity
- Diet
- Physical inactivity
- Smoking

Cancer Risk with Diabetes: Controlling for Shared Risk Factors

- Meta-analysis of studies looking at rates of colon cancer in individuals with diabetes controlling for smoking, obesity, and physical activity:
  - Men ~43%
  - Women ~35%
Diabetes and Cancer: Proposed Mechanisms

- Hyperinsulinemia
- Hyperglycemia (Warburg effect)
- Inflammation and inflammatory cytokines

Insulin Resistance, Hyperinsulinemia, and Cancer

- Insulin is a growth factor for a number of epithelial tumors
- Hyperinsulinemia reduces IGFBP-1, causing a secondary increase in IGF-1
- Changes in the insulin–IGF-1 axis may support self-sufficient growth and resistance to apoptosis
- Treatment with the insulin sensitizer metformin reduces risks of malignancies, including colon and pancreas cancer

Insulin and IGF Signaling Pathways

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Exogenous Insulin and Cancer Risk

- Subcutaneous insulin injection results in higher circulating levels of insulin than endogenous insulin secretion to achieve the same effect on blood glucose level.
- Exogenous insulin may increase cancer risk mediated by hyperinsulinemia.

Reducing Cancer Risk

- Obese women who underwent bariatric surgery were at lower risk of cancer (RR 0.58–0.62) compared to untreated obese women.
- Higher levels of physical activity have been associated with a lower risk of colon, postmenopausal breast, and endometrial cancer.
- Treatment with metformin, relative to other glucose-lowering therapies, has been associated with reduced risk of cancer and cancer mortality.

Back to Our Patient

- 58-year-old obese postmenopausal woman
- Long-standing type 2 diabetes
- Family history of both metabolic syndrome and breast cancer
- Currently treated with premix insulin
- Has read about the “cancer risk” caused by glargine
- Concerned about changing to a basal-bolus regimen with insulin glargine
Discussion Points with Patient

- Regardless of type of insulin used, the patient is at increased risk for cancer because of family history, obesity, insulin resistance, and diabetes.
- It is likely that exogenous insulin therapy does not cause cancer but higher insulin levels could promote the growth of some pre-existing cancers.
- Important that she has regular recommended cancer screenings.
- Metformin may decrease the risk of some cancers in diabetes.
- Lifestyle modification and weight loss may decrease cancer risk.
- Often less longer-term safety information is available about newer therapies so need to weigh potential risks that might not be fully understood against potential benefits. For example, in the case of newer basal insulins there is lower risk of hypoglycemia and potentially less weight gain.

Points for the Practitioner

- Interpret observational studies with caution.
- In cohort designs and randomized controlled trials, large study populations must be followed for relatively rare events to occur at high enough frequency to demonstrate an association.
- There is potential for selection bias in determining the groups to be studied in observational studies.
- Observational studies frequently have confounders that may not be recorded in the available data set, making attempts to reduce confounding difficult.
- While very popular and potentially useful, multivariate models may also be treacherous.