The 3 FDA-approved sodium glucose co-transporter 2 inhibitors remain under close post-marketing scrutiny. These 7 slides distill for you all the cancer risk information to date.

*SGLT2* Inhibitors and Cancer: What’s The Risk?

Dapagliflozin, Canagliflozin, Empagliflozin

*Farxiga  Invokana  Jardiance*

*Sodium glucose co-transporter 2*
Studies have implied that the SGLT receptor may play a role in glucose uptake in many cancers.\(^1\)

- Lung cancer metastases, but not primary tumor, have been linked to higher SGLT2 gene expression.\(^2\)
- SGLT2 inhibitors (SGLT2I) increase risk for urinary tract infections (UTIs).
- Chronic bladder irritation from recurrent or chronic UTIs could increase bladder cancer risk.\(^3\)
Confounding Factors

- Patients with diabetes already at increased risk for bladder cancer.\(^4\)
- Some antidiabetes drugs linked to cancer: pioglitazone (increased risk\(^5\)); metformin (decreased risk\(^6\)).
- Increased urinalysis related to risk of UTIs with SGLT2I use could increase detection of bladder cancer.\(^1\)
Dapagliflozin Approval Delayed

- Human trials: excess female breast, male bladder cancer seen; but **not statistically significant**.¹
- FDA **declined approval** in 2012.
- Approval 2014: new data suggested early diagnosis, **not increased incidence**, may account for excess.¹

<table>
<thead>
<tr>
<th>Cases</th>
<th>Dapagliflozin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

Human trials showed excess cases of female breast, male bladder cancer; did not reach statistical significance. FDA initially declined dapagliflozin approval in 2012. New data suggested that these excess cancers may be due to early diagnosis rather than increased incidence.
Dapagliflozin Cautions

- US Prescribing Information: advises against use in patients with active bladder cancer, cautious use if there is history.\(^7\)
- Summary of Product Characteristics: recommends against concomitant treatment with pioglitazone (linked to increased bladder cancer risk\(^7\)).

The US prescribing information advises not to use dapagliflozin in patients with active bladder cancer, and cautious use in patients with a history of bladder cancer. The Summary of Product Characteristics does not recommend using dapagliflozin in patients on pioglitazone, which has been linked to increased risk for bladder cancer.
Canagliflozin gained FDA approval in March 2013. Rat studies suggested increased risk for renal, adrenal, and Leydig cell tumors with canagliflozin use, but phase 3 clinical trials do not support increased incidence in humans.¹ FDA briefing document, Nov 2012:

- Incidence of renal, bladder, and breast cancer was low overall with canagliflozin use, with no increased incidence for canagliflozin vs controls.²
Empagliflozin gained FDA approval in August, 2014. In the FDA’s final risk evaluation and mitigation strategy review dated Nov. 12, 2013, the FDA noted a signal for lung cancer and melanoma, but most cases had known risk factors. The FDA concluded “There is no known biological mechanism to support the potential association between treatment with empagliflozin and carcinogenicity.” As the newest SGLT2 inhibitor on the market, more data may be needed to rule out the possibility of increased cancer risk with empagliflozin.
Conclusions –to-Date

- The absence of increased bladder or breast cancer risk with canagliflozin and empagliflozin may suggest that risk for these cancers is not a class effect.¹

- Evidence for the link between SGLT2 inhibitor use and cancer risk is not conclusive and remains a safety issue.¹

- Studies with larger sample size, longer exposure duration, and use of SGLT2 inhibitors in different ethnicities are needed.¹

The findings of no increased bladder or breast cancer risk with canagliflozin and empagliflozin may suggest that risk for these cancers is not a class effect. Evidence for the link between SGLT2 inhibitor use and cancer risk is not conclusive and remains a safety issue. Studies with larger sample size, longer exposure duration, and use of SGLT2 inhibitors in different ethnicities are needed.

There are 3 sodium glucose co-transporter 2 inhibitors approved for use in the US in patients with type 2 diabetes. Dapagliflozin, canagliflozin, and empagliflozin have all come under increased FDA scrutiny for potential carcinogenicity and manufacturers are engaged in mandatory post-marketing studies to further current understanding.

The brief slide show above distills the clinical data on cancer risk for the 3 SGLT2 inhibitors. References for all slides are provided below.

References:


Links: