

Risk of Renal Cell Carcinoma Following at Least 180 Days of Exposure to Canagliflozin in U.S. Patients with Type 2 Diabetes Mellitus

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Po-Yin Chang¹, Yandong Qiang¹, Jummai Apata¹, Derek J. Campbell², David J. Graham¹, Caroline Hugh², Alexis Jaquish², Maria E. Kempner², Daniel Lee¹, Andrew B. Petrone², Bahareh Rasouli³, Fatma M. Shebl¹, Rongmei Zhang¹, Sophie E. Mayer³

¹Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA; ²Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston, MA, USA; ³Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA



Conflict of Interest and Acknowledgement

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Background

In the Canagliflozin Cardiovascular Assessment Study (CANVAS), risk of renal cell carcinoma (RCC) was numerically higher in the canagliflozin arm (0.29%, 8/2716) than placebo arm (0.15%, 2/1331), excluding subjects with <6 months of follow-up, <90 days of treatment, or a history of RCC. Number of RCC events was small.

Objective

To investigate the risk of RCC in adult patients with type 2 diabetes mellitus (T2DM) adhering to the treatment strategies of at least 180 days of exposure to canagliflozin versus sitagliptin in the first year after initiation.

Methods

Data Source: Claims data from six Data Partners (DP) of the U.S. FDA Sentinel System
Study Period: March 1, 2013 – March 31, 2025
Study Population: New users of canagliflozin or sitagliptin aged ≥18 years with T2DM, who had ≥365 days of continuous insurance coverage, no evidence of kidney cancer or nephrectomy in all available history, and who met all the following additional criteria in the 365 days before the index date of the first dispensing of a study drug:

- Dispensing of an oral antidiabetic drug
- No evidence of type 1 diabetes, chronic kidney disease (CKD) stages III-V, dialysis, or use of glucagon-like peptide-1 receptor agonists (GLP-1RAs)
- No use of any study drugs in 365-day before the index dispensing

Study Drug Exposure: Identified via National Drug Codes in outpatient dispensing data. Days of exposure were based on cumulative dispensed days’ supply with no gaps allowed.

Incident RCC Algorithm: Composite of early- and late-stage RCC, requiring evidence of ≥2 diagnosis codes, diagnostic work-up, and stage-appropriate treatment (or mortality)

At-risk Follow-up began on Day 1 after index date until the earliest of RCC, death, disenrollment, evidence of CKD stages III-V, dialysis, or initiation of comparator drug class

Statistical Analyses: A clone-censor-weight approach was used to estimate the hazard ratio (HR) that would have been observed if canagliflozin initiators had been randomized to the treatment strategy of ≥180 days of canagliflozin versus sitagliptin in the first year of follow-up

- Cloning:** All initiators were cloned and assigned to <180-day and ≥180-day treatment strategies
- Censoring:** Adherence to the treatment strategy of interest for each clone was assessed during four 90-day intervals in the first 360 days of follow-up, along with time-varying predictors of adherence and RCC. Clones deviating from their assigned treatment strategy were artificially censored at interval end
- Weighting:** Baseline treatment propensity scores were used to balance canagliflozin and sitagliptin initiator cohorts and estimate the average treatment effect in the treated (ATT, canagliflozin initiators). Inverse-probability-of-censoring weights (IPCW), estimated conditional on baseline covariates and time-varying predictors of adherence and RCC risk, were used to account for selection of adherent clones
- Outcome modeling:** Cox proportional hazards modeling was used to produce unweighted and weighted HRs. Bootstrapped 95% confidence intervals (CIs) were computed at each DP and results meta-analyzed

Subgroup and Sensitivity Analyses:

- Censoring at non-RCC malignancy, censoring at GLP-1RA or insulin initiation
- Using secondary exposure (any sodium-glucose cotransporter-2 inhibitor) and outcome definitions
- Analyses stratified by sex, age <65 years, and baseline obesity status

Results

Table 1. Eligible Initiators of canagliflozin and sitagliptin

Covariates (N [%], or mean ± SD)	Unweighted Cohorts		Crude SMD	ATT-weighted SMD
	Canagliflozin (n=159,011)	Sitagliptin (n=921,012)		
Baseline Covariates				
Age (years), mean	60.7 ± 10.3	65.2 ± 11.1	-0.426	-0.008
Female	76,097 (47.9)	488,148 (53.0)	-0.103	0.000
Retinopathy	17,321 (10.9)	114,626 (12.4)	-0.048	-0.000
Nephropathy	12,727 (8.0)	104,227 (11.3)	-0.112	-0.003
Obesity	56,369 (35.4)	278,426 (30.2)	0.111	0.003
Insulin	43,470 (27.3)	150,695 (16.4)	0.268	0.012
Diabetes severity score, mean	1.3 ± 1.5	1.5 ± 1.7	-0.166	-0.008
CCS, mean	1.2 ± 2.0	1.7 ± 2.5	-0.235	-0.020
Post-index Covariates Assessed During All Available Follow-up Time				
GLP-1RA initiation	34,282 (21.6)	127,557 (13.8)	0.203	0.141
Insulin initiation	20,015 (12.6)	143,314 (15.6)	-0.086	-0.047

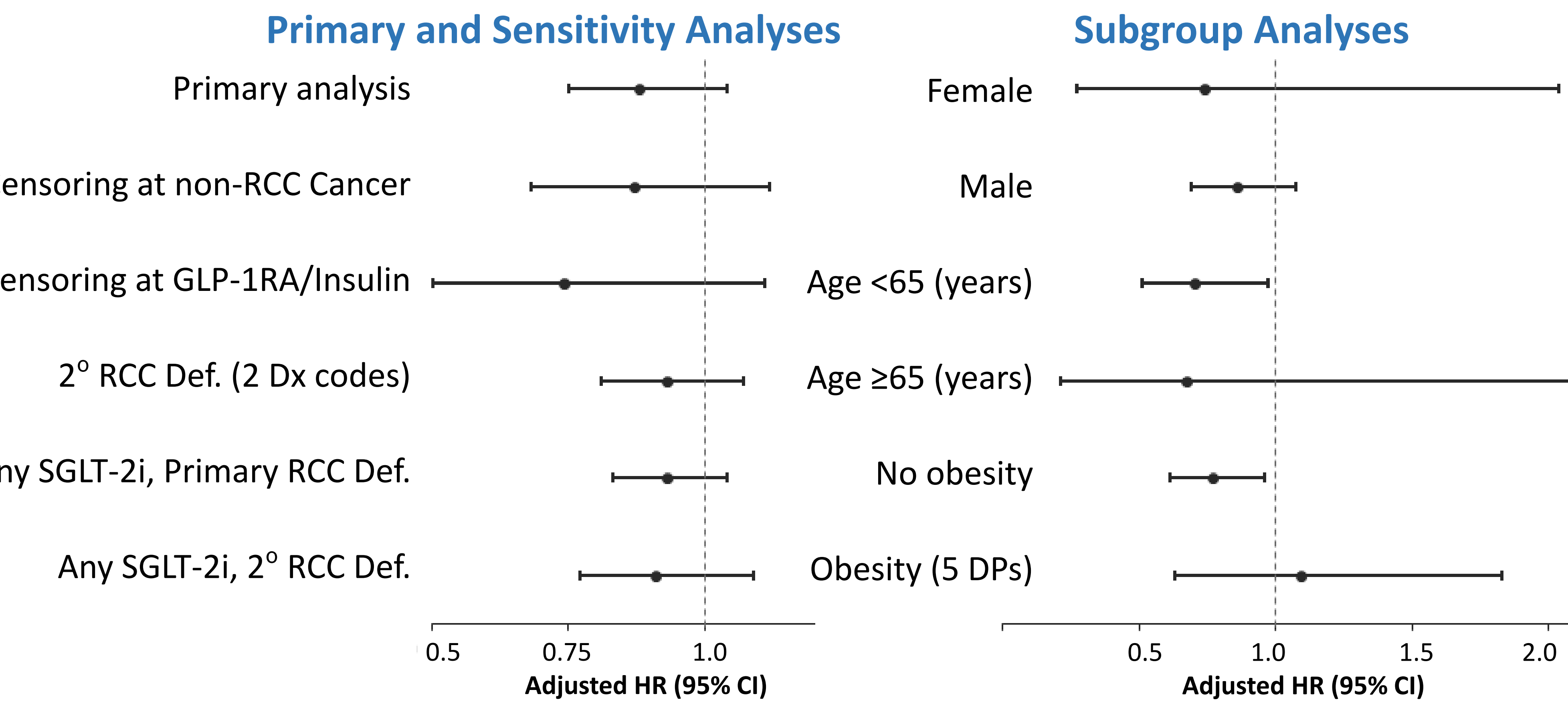
SD standard deviation; CCS Combined comorbidity score; SMD standardized mean difference

Analytic cohorts for clone-censor-weighting design:

- 111,295 canagliflozin and 693,703 sitagliptin initiators contributed data to the ≥180-day treatment strategies
- Approximately 20% of each cohort was censored or experienced an event before definitive treatment strategy assignment
- On day 360 after ATT/IPCW, covariates were largely balanced
- Insulin initiation during the first year: Less common in the canagliflozin cohort (4% vs 6%, SMD: -0.102)

Table 2. Number, Incidence, and Hazard Ratio for RCC Events

Treatment strategy	Clones	Total At-Risk PY	Average At-Risk PY	RCC Events	Incidence/ 10,000 PY	Hazard Ratio (95% CI)
Unweighted						
≥ 180 days CANA	111,295	348,936.72	3.14	193	5.53	0.88 (0.70, 1.11)
≥ 180 days SITA	693,703	1,874,154.29	2.70	1,143	6.10	Reference
ATT/IPC Weighted (1% weight truncation)						
≥ 180 days CANA	158,630	498,875.99	3.14	280	5.61	0.88 (0.75, 1.04)
≥ 180 days SITA	157,577	453,739.40	2.88	289	6.38	Reference



ATT average treatment effect in the treated; CANA canagliflozin; CI confidence interval; Def. definition; DP Data Partner; Dx diagnosis; IPCW inverse-probability-of censoring weighting; PY person-years; RCC renal cell carcinoma; SGLT-2i sodium-glucose cotransporter-2 inhibitor; SITA sitagliptin; 2°secondary.

Conclusions

- Incidence rate of RCC was 5.61 to 6.38 cases/10,000 person-years (PY) in the weighted ≥180 treatment strategy cohorts. In CANVAS trials, RCC rate was 6 cases/10,000 PY (<https://www.nejm.org/doi/full/10.1056/NEJMoa1611925>).
- Our study did not observe an increased risk of RCC over an average follow-up of approximately 3 years among canagliflozin initiators, assuming full adherence to the treatment strategies of interest under a hypothetical randomized comparison of canagliflozin versus sitagliptin.
- Results from subgroup and sensitivity analyses were consistent.
- Limitations:** Misclassification of exposures and covariates are possible and probably nondifferential. Increased detection of RCC among canagliflozin users (e.g., due to labeling) could lead to an overestimated risk but no increased risk was observed. Impact of unbalanced GLP-1RA initiation during follow-up was unclear. This study was unable to assess longer exposure durations. Competing risks and more complex treatment strategies were not considered.