Risk of Non-Melanoma Skin Cancer Associated with Hydrochlorothiazide-Containing Products in the United States

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Disclosures

- No external funding to disclose

- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA

Consistent Elevated Risk of SCC with Hydrochlorothiazide in the Literature

AUTHOR, COUNTRY, YEAR	DATA SOURCES	ODDS RATIOS (95% CI)		
		BCC	SCC	MM
Jensen et al., Denmark, 2008	DCR, DCRS (North Jutland only)	1.05 (0.95-1.16) 1.10 (0.95-1.26)[a]	1.58 (1.29-1.93) 1.92 (1.46-2.54)[a]	1.32 (1.03-1.70) 1.24 (0.86-1.78)[a]
Schmidt et al, Denmark, 2015	DCR, DCRS Northern Denmark only)	1.23 (1.12-1.35)	2.68 (2.24-3.21)	1.02 (0.78-1.33)
Pottegård et al, Denmark, 2017	DCR, DCRS	NR	2.1 (1.7-2.6)	NR
Pedersen et al, Denmark, 2017	DCR, DCRS	1.08 (1.05-1.10)	1.75 (1.66-1.85)	NR
EMA-Sponsored Study[b]	THIN	IRR[c]: 1.30 (1.03-1.65)	IRR[c]: 2.93 (1.85–4.62)	IRR[c]: 0.90 (0.33–2.45)

BCC: Basal Cell Carcinoma; SCC: Squamous Cell Carcinoma; MM: Malignant Melanoma; HCTZ: Hydrochlorothiazide; DCR: Danish Cancer Registry; DCRS: Danish Civil Registration System; THIN: The Health Improvement Network; IRR: Incidence Rate Ratio

[a]Odds ratio when prescriptions issued within 5 years of diagnosis date were excluded

[b]EMA-sponsored study presented at the 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; August 24-28, 2019

[c]Associations reported for with high-dose cumulative HCTZ exposure

Study Objectives

- To examine the risk of NMSC among patients exposed to HCTZ compared to patients who received ACEI in a large US population.
  - Is there a dose-response relationship between the use of HCTZ-containing products and the risk of non-melanoma skin cancer?

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Data source

- 17 health plans participating in the Sentinel System
  - 15 national or regional insurers
  - 1 state Medicaid
  - 100% Medicare fee-for-service plan

- Study period
  - January 1, 2000 to August 31, 2018

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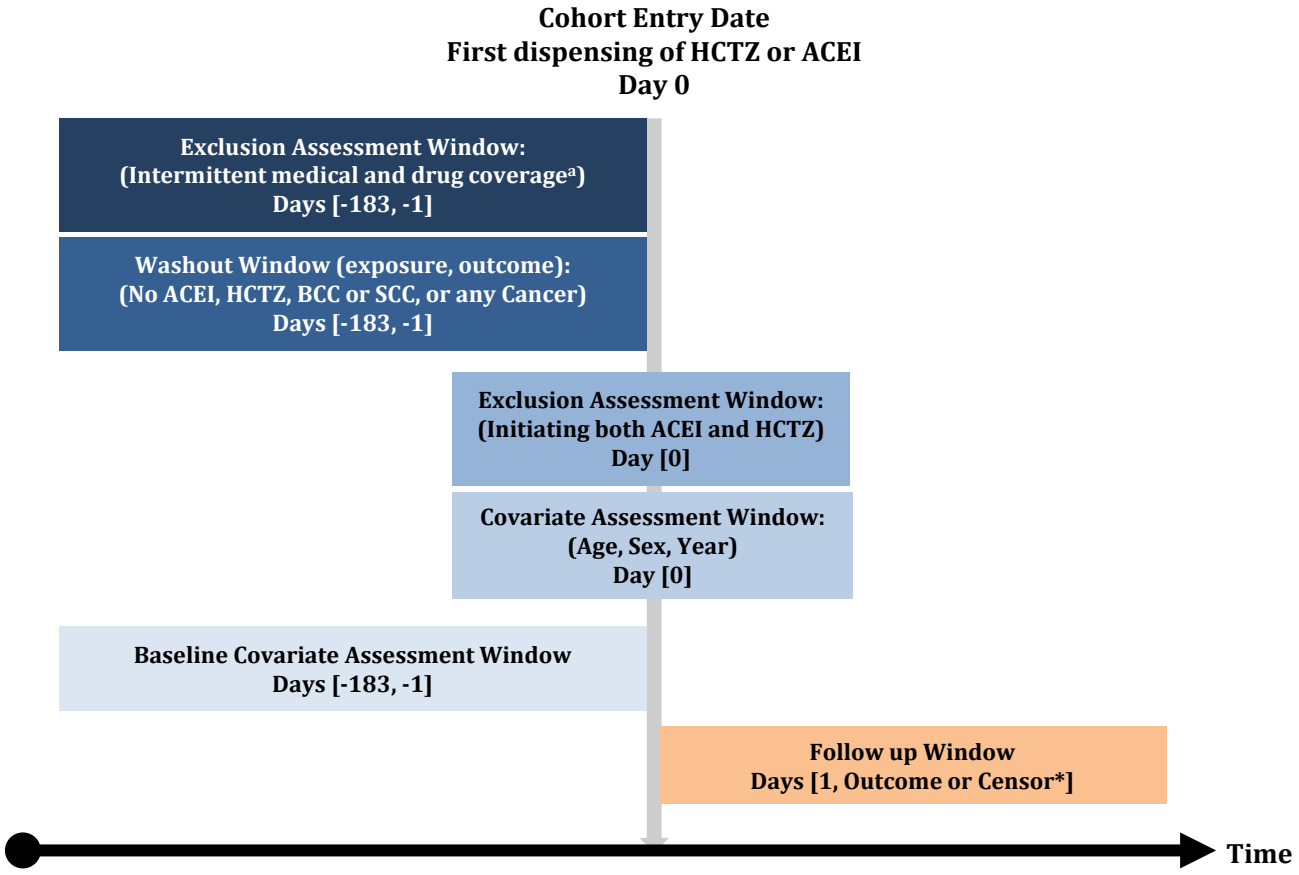
Study design



*Censoring criteria: Disenrollment, study end date, end of data availability, diagnosis of non-outcome cancer, use of chemotherapy or radiation therapy, or death

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Exposure

- HCTZ-containing products

- Cumulative dose categories
  - <10,000mg
  - 10,000 – 24,999mg
  - 25,000 – 49,999mg
  - 50,000 – 74,999mg
  - 75,000 – 99,999mg
  - ≥100,000mg

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Outcome

- Non-melanoma skin cancer
  - Basal cell carcinoma
  - Squamous cell carcinoma
- ICD-9-CM codes (ICD-9-CM: 173.xx or ICD-10-CM: C44.xxx) plus a procedure code for excision, destruction, Mohs microscopic chemosurgery, or Mohs excision technique, or a NDC for a topical chemotherapy treatment on or within 30 days after the diagnosis date

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Potential confounders

- Demographic factors
- Risk factors for BCC and SCC
  - High-risk skin conditions
  - Other photosensitivity medications
  - Medications with suggest cancer protective effects
  - Ultraviolet exposure

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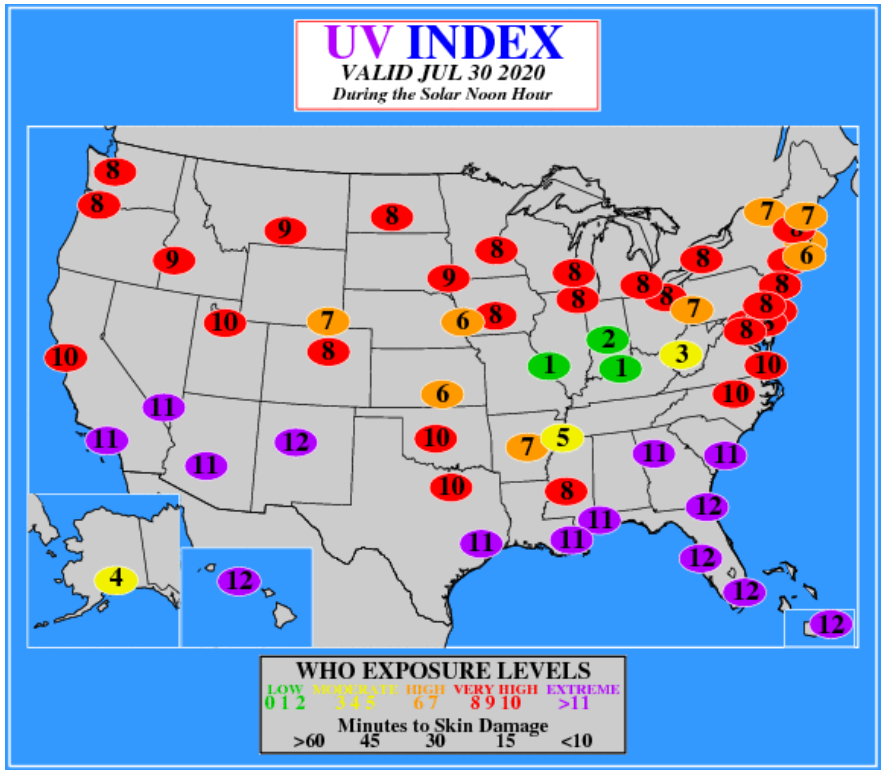
Adjustment of UV Exposure

- Annual maximum median clear sky ultraviolet index was obtained for each state over the study period.
- For states with multiple cities (Florida, Texas, Pennsylvania, and New York), highest median selected to represent the state.
- Categorized ultraviolet index as low (0, 1, 2), moderate (3, 4, 5), high (6, 7), very high (8, 9, 10), and extremely high (≥11) according to the World Health Organization ultraviolet index reporting categories



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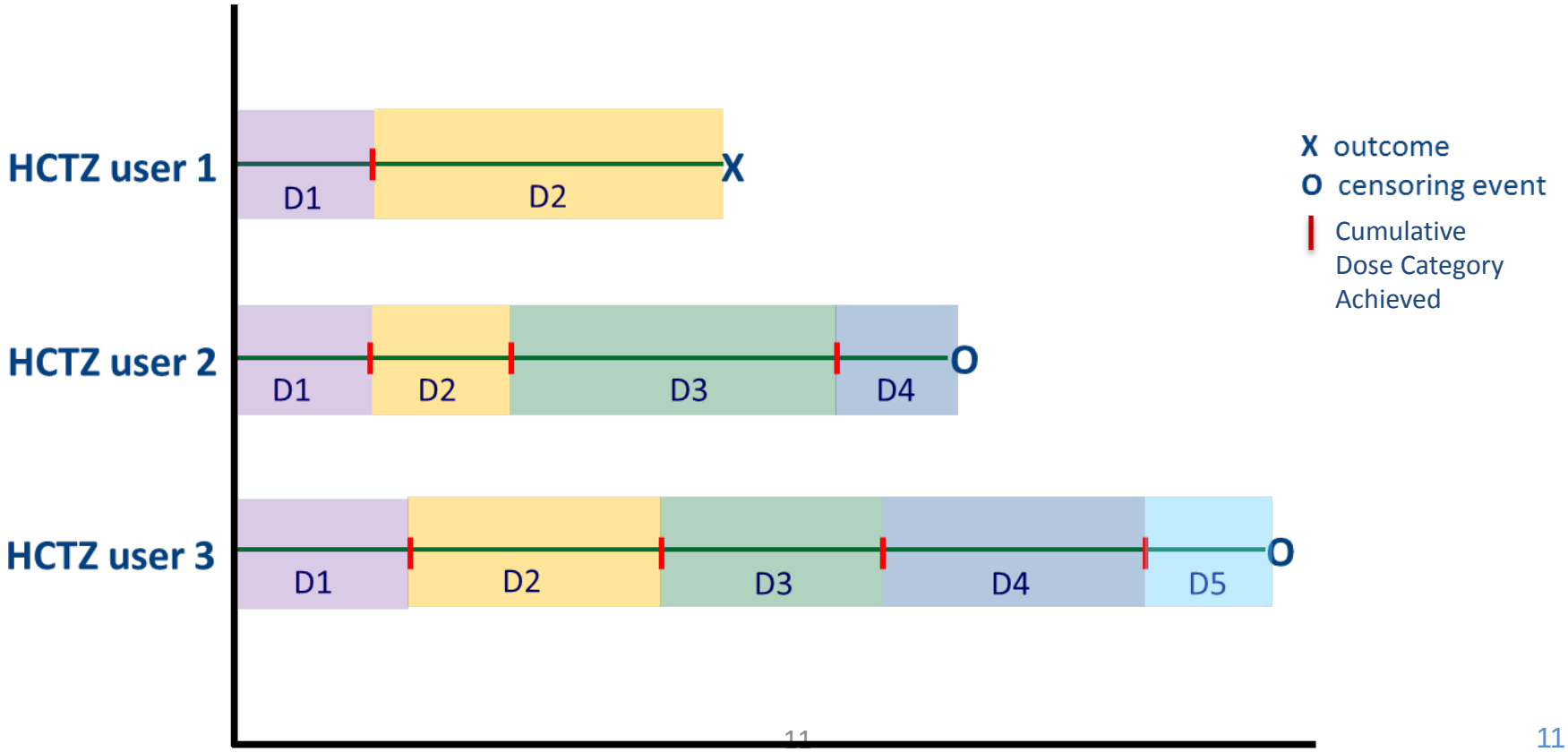
Dose-response Analysis

- Update cumulative dose over time (time-varying) and assign person-time to a particular dose category



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Sensitivity analysis

- Excluding outcomes occurring in the first 2 years
- Defining outcome over a 60-day period
- Defining outcome over a 180-day period

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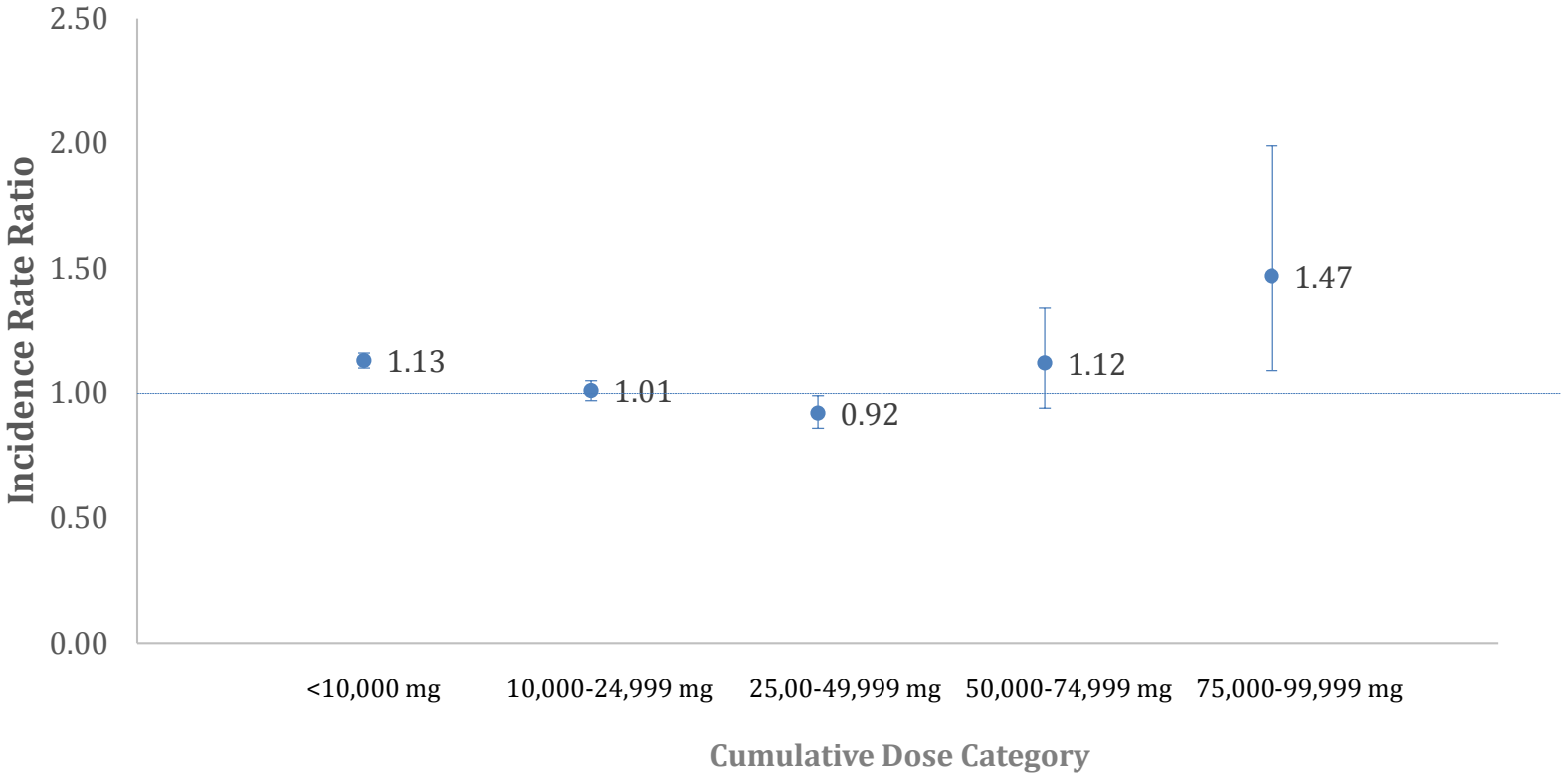
Baseline Differences

- Over 6 million HCTZ and 7 million ACEI new users who met eligibility criteria
  - Over 5 million HCTZ and ACEI users were matched
- ACEI users slightly older (mean: 61.6 vs. 59.8 years); more males (53.5% vs. 38.5%)
- ACEI users had higher combined comorbidity score (mean: 2.2. vs. 1.4); more CVD-related diagnosis (2.9% vs. 1.2%) and more diabetes diagnosis (35.8% vs. 18.7%)
- More HCTZ users resided in areas with High UV index (43.2% vs. 39.1%)
- After propensity score matching, all covariates were balanced with SMD ≤0.01

Incidence Rates per 1000 person-years

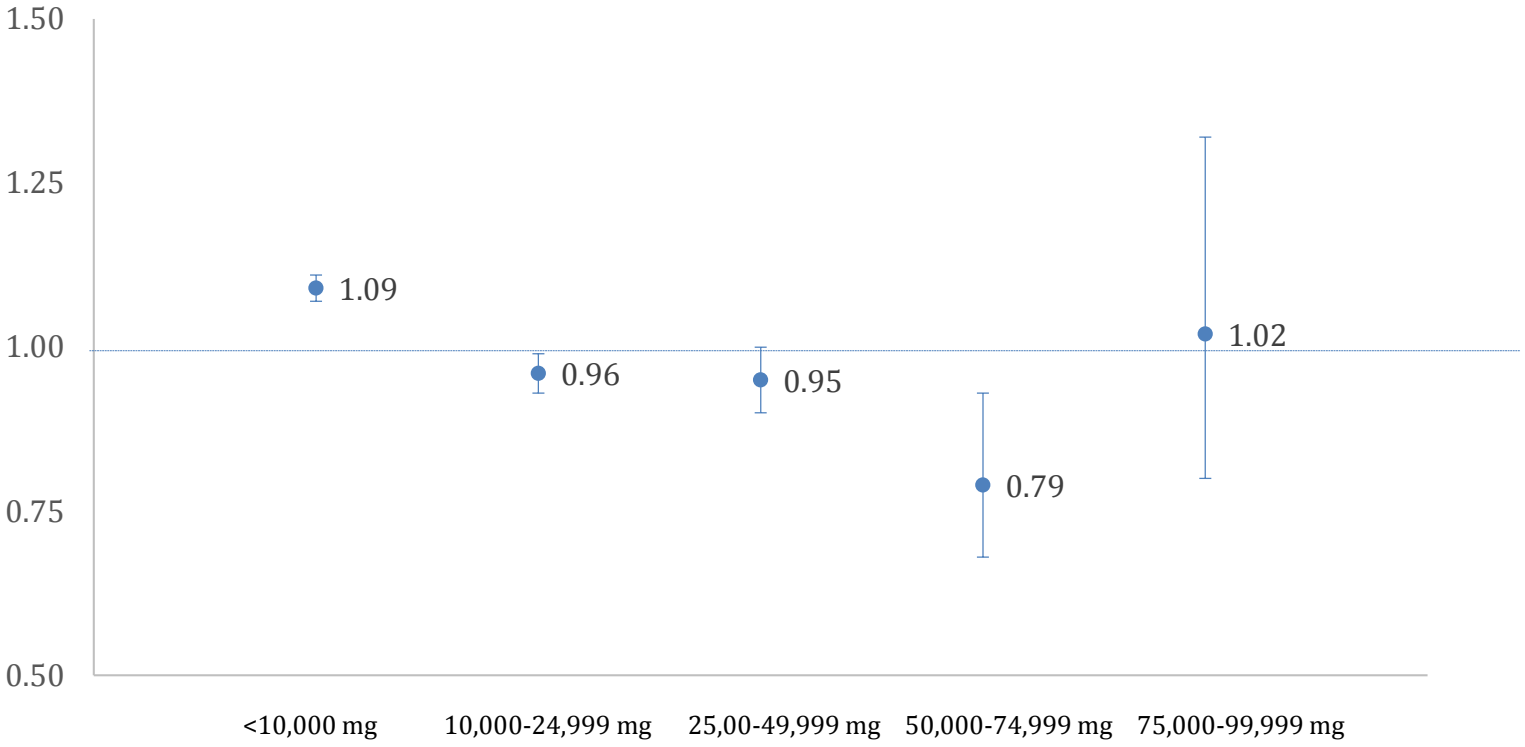
	BCC Rates			SCC Rates		
	HCTZ	ACEI	HR (95% CI)	HCTZ	ACEI	HR (95% CI)
Overall	2.78	2.82	0.99 (0.97, 1.00)	1.66	1.60	1.04 (1.02, 1.06)
Male	3.33	3.35	0.99 (0.97, 1.01)	1.89	1.78	1.06 (1.03, 1.09)
Female	2.30	2.37	0.98 (0.95, 1.00)	1.47	1.46	1.01 (0.98, 1.04)
Age (years)						
<50	0.50	0.57	0.88 (0.82, 0.94)	0.13	0.14	0.92 (0.80, 1.00)
50-59	1.52	1.67	0.91 (0.88, 0.95)	0.55	0.61	0.91 (0.85, 0.98)
60-74	3.78	3.84	0.99 (0.97, 1.01)	2.10	2.01	1.05 (1.02, 1.08)
75+	6.04	6.02	1.01 (0.98, 1.03)	4.69	4.52	1.04 (1.01, 1.07)
Race						
White	4.48	4.12	1.09 (1.07, 1.11)	2.92	2.55	1.15 (1.12, 1.17)
Black	0.04	0.05	0.83 (0.55, 1.27)	0.04	0.05	0.84 (0.54, 1.30)
Asian	0.14	0.08	1.72 (1.13, 2.61)	0.07	0.10	0.72 (0.44, 1.15)
Pacific Islander	0.27	0.25	1.09 (0.54, 2.21)	0.22	0.13	1.69 (0.70, 4.09)
American Indian	1.31	0.81	1.58 (1.06, 2.35)	0.44	0.48	0.95 (0.52, 1.72)
Unknown	1.91	1.99	0.96 (0.93, 0.99)	0.86	0.85	1.02 (0.98, 1.06)

Increased SCC risk at higher cumulative doses



Percent of HCTZ users	100	25.6	8.2	1.9	0.6
Follow-up (7 years+) (%)	5.7	22.7	61.6	90.5	96.4

No increased BCC risk at higher doses



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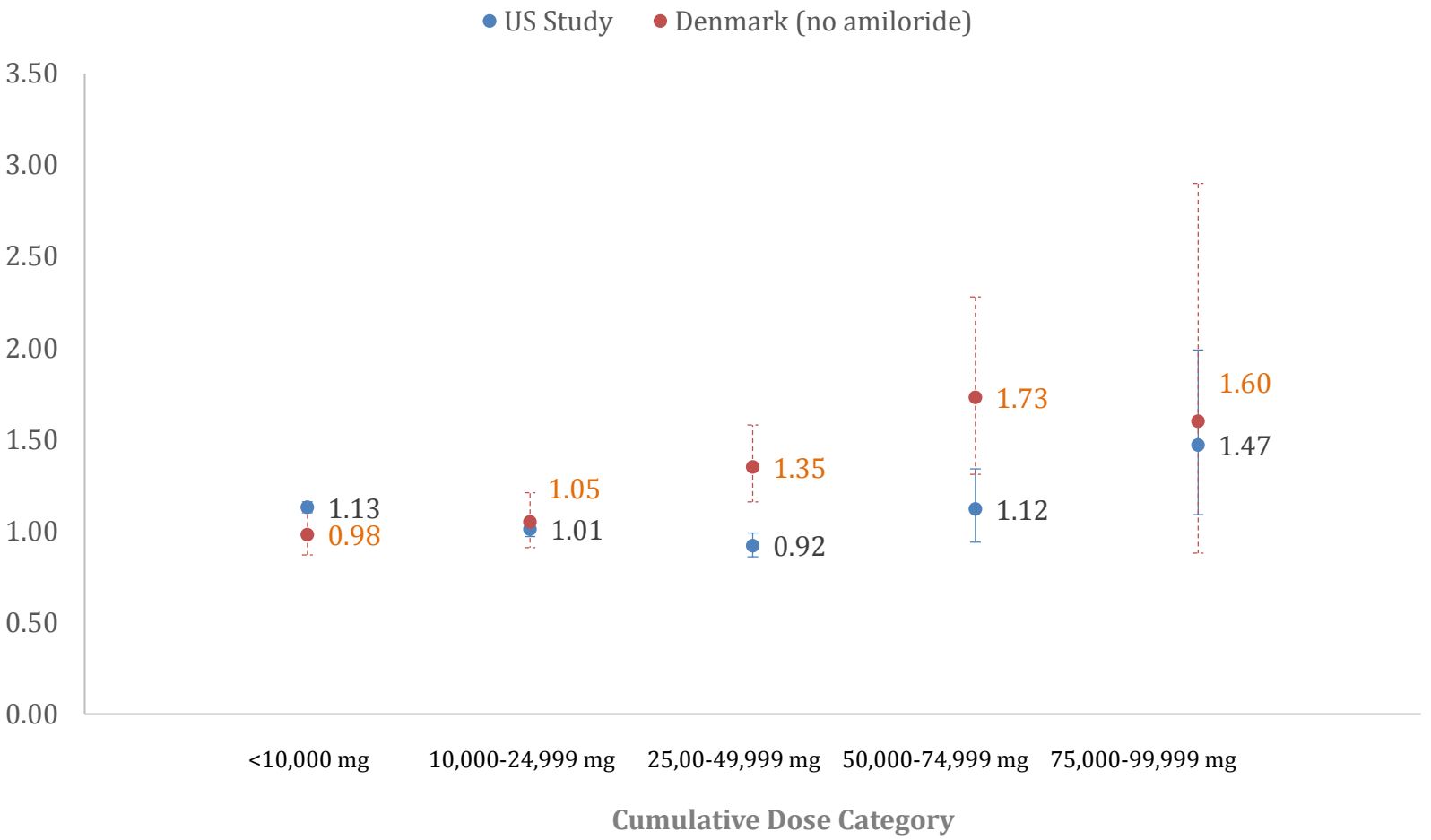
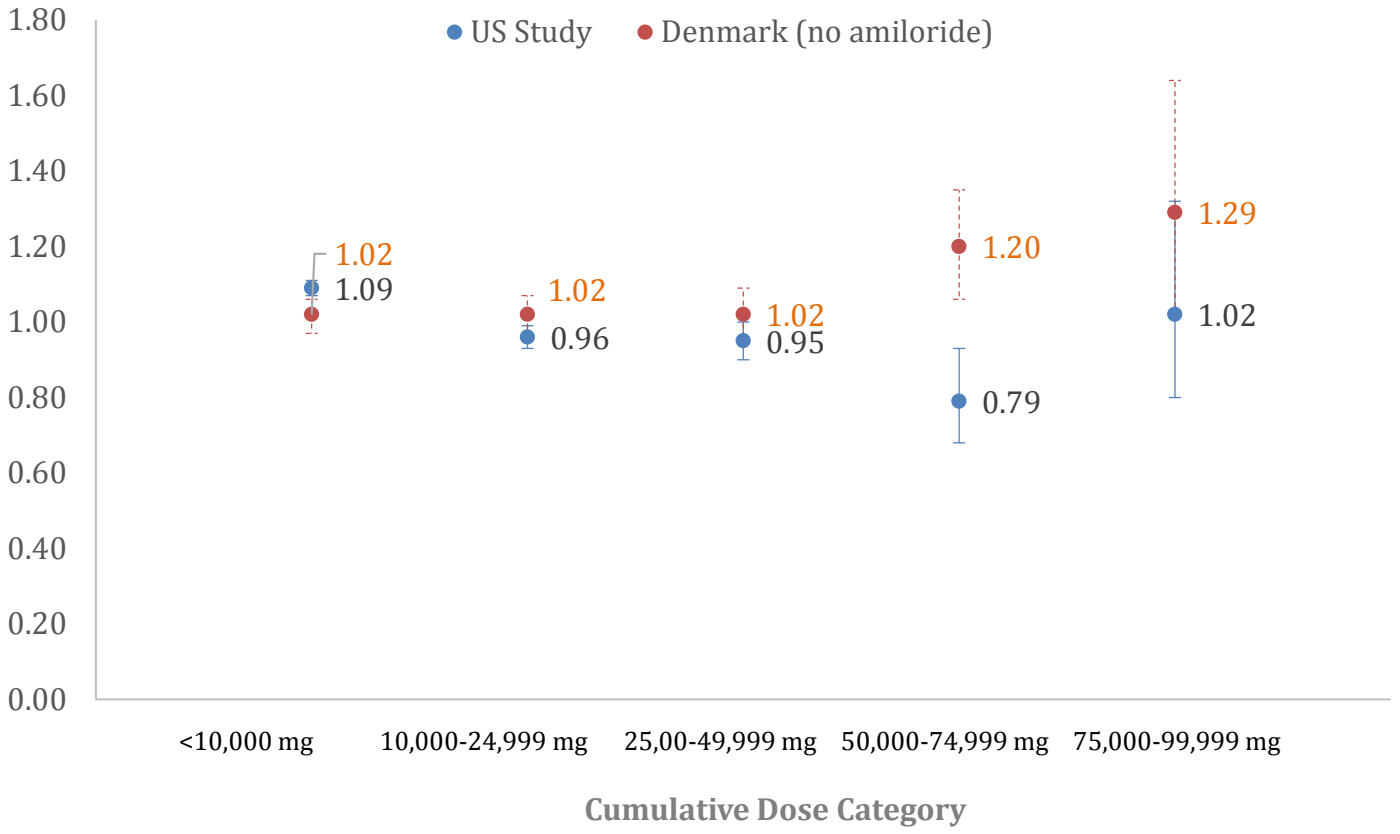
SCC Risk for US and Danish Populations



US Study restricted to Caucasian population; Denmark effect estimates restricted to non-users of amiloride (Pedersen SA, et al (2018). Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark.

BCC Risk for US and Denmark Populations



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Discussion

- No increased risk observed in overall population but this is likely due to low proportion of patients exposed to high cumulative dose
- Overall high incidence of BCC compared to SCC is consistent with previous studies
  - Over 90% of NMSC is BCC
- Presence of increased SCC risk associated with HCTZ and absence of BCC risk with HCTZ is also consistent with previous studies
- Risk significant among white racial group

Differences in Effect Estimates

- HCTZ combinations

National HCTZ Utilization (Denmark)[a]		National HCTZ Utilization(US)[b]	
Combination	%	Combination	%
HCTZ-ARB	44	HCTZ (single)	43
HCTZ-amiloride	33	HCTZ-ACEI	25
HCTZ-ACEI	21	HCTZ-ARB	24
		HCTZ-triamterene	9
		HCTZ-amiloride	0.1

Comparison of US HCTZ utilization to Denmark HCTZ utilization

[a]Utilization data was retrieved from Pottegard et al[1], 2004-2012

[b]IQVIA™ Total Patient Tracker Database. Year 2017. Accessed April and May 2018.

- Cumulative dose analysis (≥50,00mg) Follow-up
  - 7 years plus vs. 10 years plus

Discussion

- Strengths of the study
  - Large sample size that enabled dose-response relation analysis
  - Geographically and demographically diverse population
  - Adjustment for proxies for ultraviolet exposure
  - Use of a validated outcome algorithm

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Discussion

- Limitations of the study
  - Inability to capture non-medically attended outcome events
  - Small proportion of patients with high cumulative HCTZ dose (3%)
  - Inability to study long term impact of lower cumulative doses
  - Non-negligible missing race information
  - No complete information on cancer location

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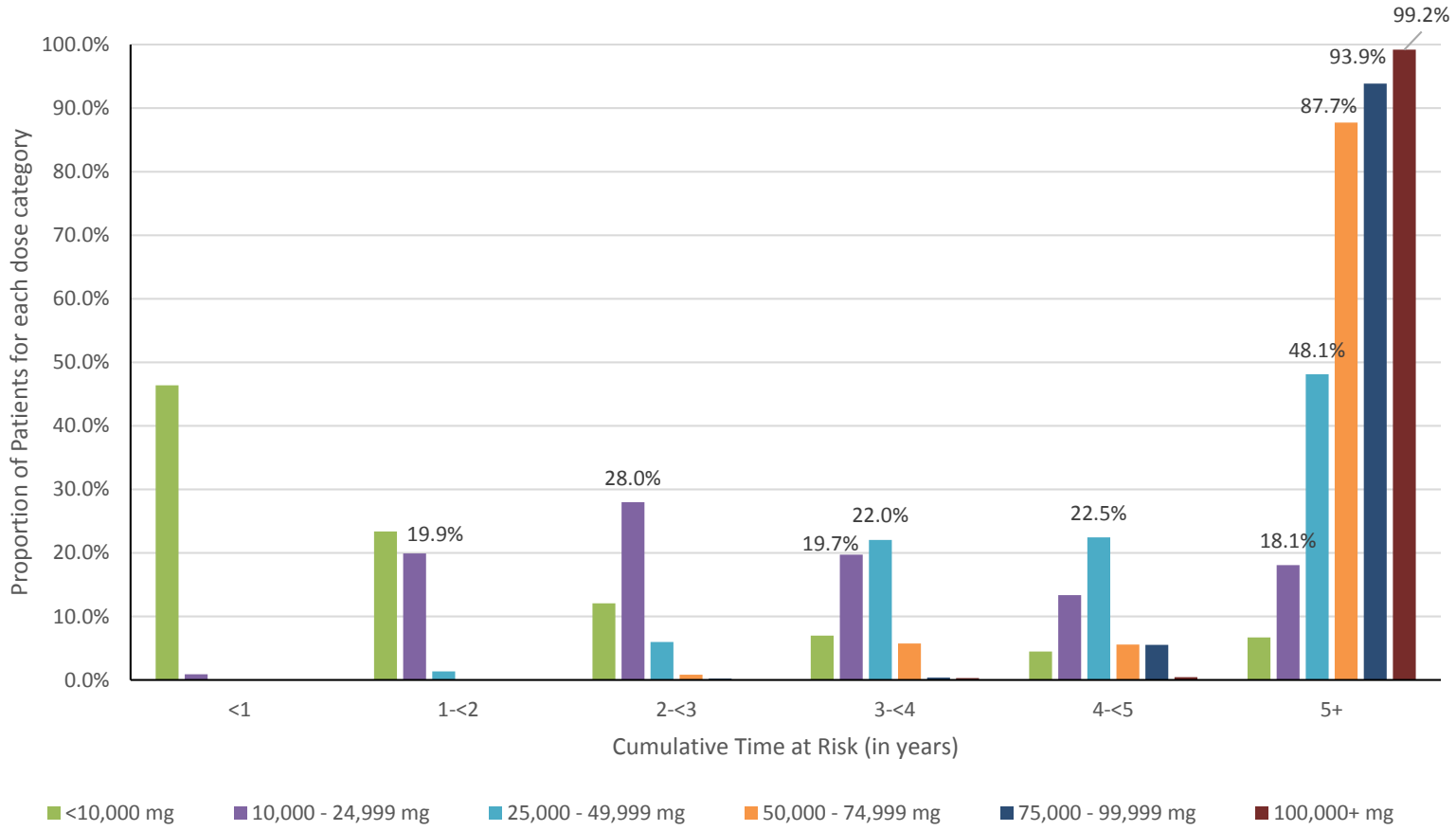
Total time at risk stratified by cumulative dose category



Distribution of Final HCTZ Dispensed Strength by Cumulative Dose Category

HCTZ Dispensing Strength	Overall n=5,211,321	Dose Group 1 <10,000mg n=3,874,786	Dose Group 2 10,000-24,999mg n=908,742	Dose Group 3 25,000-49,999mg n=330,736	Dose Group 4 50,000-74,999mg n=63,764	Dose Group 5 75,000-99,999mg n=19,267	Dose Group 6 100,000+mg n=14,026
6.25 mg	1.3	1.6	0.3	0.0	0.0	0.0	0.0
12.5 mg	36.6	42.5	25.3	9.5	2.6	1.1	0.2
15 mg	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25 mg	57.1	52.6	67.7	78.1	71.0	58.5	37.7
30 mg	0.0	0.0	0.0	0.0	0.0	0.0	0.0
50 mg	5.0	3.3	6.7	12.3	26.4	40.4	62.0
100 mg	0.0	0.0	0.0	0.0	0.0	0.0	0.0