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Hydrochlorothiazide use and risk of keratinocyte carcinoma and melanoma: A multi-site population-based cohort study

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CAPSULE SUMMARY

- In this multi-site population-based cohort study, increased risks of keratinocyte carcinoma or melanoma were observed with longer duration of use and higher cumulative doses of hydrochlorothiazide.
- Given the importance of hydrochlorothiazide in the treatment of hypertension, physicians, patients, and decision-makers must weigh its benefits and risk compared with other antihypertensive drugs.

ABSTRACT

Background: The association between hydrochlorothiazide (HCTZ) and skin cancer remains controversial.

Objective: To determine whether HCTZ is associated with an increased risk of skin cancer compared with angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs).

Methods: Two new-user, active comparator cohorts were assembled using six Canadian databases. Site-specific hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using standardized morbidity ratio weighted Cox proportional hazard models and pooled using random-effects meta-analysis.

Results: HCTZ was not associated with an overall increased risk of keratinocyte carcinoma compared with ACEIs or CCBs, although increased risks were observed with longer durations (≥10 years; HR: 1.12; 95% CI: 1.03-1.21) and higher cumulative doses (≥100,000 mg; HR: 1.49; 95% CI: 1.27-1.76). For melanoma, there was no association with ACEIs, but a 32% increased risk with CCBs (crude incidence rates: 64.2 vs. 58.4 per 100,000 person-years; HR: 1.32; 95% CI: 1.19-1.46; estimated number needed to harm at 5 years of follow-up: 1,627 patients), with increased risks with longer durations and cumulative doses.

Limitations: Residual confounding due to the observational design.

Conclusions: Increased risks of keratinocyte carcinoma and melanoma were observed with longer durations of use and higher cumulative doses of HCTZ.

INTRODUCTION

Hydrochlorothiazide (HCTZ) is among the most widely used antihypertensive drugs,[1-3] which is recommended as a first-line treatment for hypertension.[4] However, this thiazide diuretic has photosensitizing properties that may induce an abnormal skin response to ultraviolet light,[5] raising concerns that it may increase the risk of skin cancer.

Several observational studies have investigated whether HCTZ is associated with an increased risk of malignant melanoma and keratinocyte carcinoma (including basal cell carcinoma [BCC] and cutaneous squamous cell carcinoma [cSCC]).[6-21] Overall, these studies generated mixed findings, with some reporting positive associations with certain skin cancers,[6-9,12,14-21] while others reporting null associations.[10,11,13,16,18] These discrepant findings may be due to methodological limitations in some of these studies, including potential confounding by indication, detection bias, and time-window bias. While regulatory agencies have issued safety warnings of the possible risks of keratinocyte carcinoma with use of HCTZ,[22-24] its potential association with melanoma remains uncertain.

Thus, at the request of Health Canada, we conducted a large multi-site population-based cohort study to determine whether HCTZ is associated with an increased risk of keratinocyte carcinoma and melanoma, separately, compared with two clinically-relevant comparators, angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs).

METHODS

Data Sources

We conducted a multi-site population-based cohort study using administrative health databases from six Canadian provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan). Our data sources were physician service claims, hospital discharge abstracts, prescription drug claims, provincial cancer registries, and the provincial health insurance registry in each province.

Study Population

In each jurisdiction, we assembled two new-user, active comparator cohorts, where initiators of HCTZ were compared with initiators of ACEIs in the primary comparison and with initiators of CCBs in the secondary comparison between April 1, 1995, and March 31, 2018 (or the latest date of data availability at each site minus one year for latency purposes; **eTable 1**). Cohort entry was defined by the first dispensation of either HCTZ or the corresponding comparator drug. These comparator groups were chosen to reduce confounding by indication, as both drug classes are indicated as possible first-line treatments for hypertension.[4]

To be included, patients were required to be 40 years and older (or 66 years and older in Alberta, Nova Scotia, and Ontario) and to have at least 365 days of health insurance coverage before cohort entry. We excluded patients with a prescription drug claim for any antihypertensive drug at any time before cohort entry; thus, the exposure groups represented patients newly treated for hypertension with a study drug (alone or in combination with other antihypertensive drugs). We also excluded patients with a history of any skin cancer (defined below), human immunodeficiency virus infection, or solid organ transplantation at any time or

365 days before and including cohort entry. Lastly, patients were required to have a minimum of 365 days of follow-up after cohort entry to consider a minimum cancer latency period between treatment initiation and the outcomes (i.e., lag period).

All patients were followed starting 365 days after cohort entry (i.e., after the lag period) until an incident diagnosis of one of the study outcomes (defined below) or censored 365 days after switching (or adding on) to another study drug, death from any cause, end of health insurance coverage or end of the study period at each site, whichever occurred first.

Study Outcomes

In the sites with access to provincial cancer registries, incident invasive keratinocyte carcinoma (Manitoba and Saskatchewan) and melanoma (Manitoba, Ontario, and Saskatchewan) were defined using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) morphology codes (**eTable 2**). In the remaining sites, skin cancers were identified by adapting a validated algorithm combining diagnostic codes with related surgical procedures within 180 days of each other (**eTables 3-4**).[25] The earliest diagnosis or procedure date defined the outcome event type and date. Patients diagnosed with both types of skin cancer on the same date were assigned both outcomes. Additionally, keratinocyte carcinoma was further subclassified into BCC and cSCC subtypes using provincial cancer registries and ICD-O-3 morphology codes in Manitoba and Saskatchewan. If BCC and cSCC occurred on the same date, the event was defined as cSCC.

Potential Confounders

We considered 33 potential confounders, all assessed before or at cohort entry. These included demographic variables, comorbidities, prescription drugs, markers of healthcare utilization, and markers of health-seeking behaviors (**eTable 5**). Age was modeled as a continuous variable using restricted cubic splines to account for a possible non-linear relation with the exposures.[26]

Statistical Analysis

We used multivariable logistic regression to estimate calendar-time-specific propensity scores (PS) of receiving HCTZ versus the comparator drugs conditional on the covariates described above.[27] Calendar-time-specific PS aimed to account for secular trends in prescribing patterns, variations in ultraviolet exposure patterns, and possible heterogeneity in covariate distributions during the study period. We used the estimated PS to calculate standardized morbidity ratio weights (SMRWs) to balance the exposure groups.[28] SMRWs were obtained by assigning a weight of one to HCTZ users and a weight equal to the odds of the treatment probability (PS/(1-PS)) for the comparator groups. The estimand generated by this analysis is the average treatment effect among the treated.[28]

Descriptive statistics were used to summarize baseline characteristics before and after weighting. Covariate balance was assessed using standardized mean differences, with an absolute value of less than 0.10 indicative of good balance.[29] Site-specific crude incidence rates of skin cancer and corresponding 95% confidence intervals (CIs) based on the Poisson distribution were calculated for each exposure group. Cox proportional hazards models weighted by SMRW, with calendar year as a stratification variable, were fit to estimate site-specific hazard

196 ratios (HRs) and corresponding 95% CIs with robust variance estimators. The number needed to
197 harm (NNH) were calculated for both outcomes at 5 and 10 years of follow-up using the Kaplan-
198 Meier method accounting for varying follow-up times.[30]
199
200 *Secondary and Sensitivity Analyses*
201 We conducted five secondary analyses in each cohort. First, we repeated the primary
202 analysis using an on-treatment exposure definition whereby patients were followed while
203 continuously exposed to the cohort entry drug until treatment discontinuation or switching to the
204 comparator drug. A one-year grace period was used in the event of non-overlapping prescriptions
205 to account for possible diagnostic delays. Second, we assessed whether the association increased
206 with cumulative duration of use by summing the prescription durations of both HCTZ and the
207 comparator drug in a time-varying fashion (<1, ≥1 to <3, ≥3 to <5, ≥5 to <10, and ≥10 years).
208 Third, we conducted a time since initiation analysis, defined as the time between cohort entry
209 and outcome event dates (<3, ≥3 to ≤5, and >5 years). Fourth, we assessed whether there was a
210 dose-response relation by summing the total dose associated with each HCTZ prescription in a
211 time-varying fashion (<50,000, ≥50,000 to <100,000, and ≥100,000 mg). Finally, we assessed
212 effect modification by age (≤65, 66-74, and ≥75 years), sex, and immunosuppressive status.
213 We conducted three sensitivity analyses to assess the robustness of our findings. First, we
214 used inverse probability of censoring weighting to account for possible informative censoring
215 due to switching, death from any cause, or occurrence of the alternate skin cancer outcome
216 during follow-up. Second, we repeated the analyses by extending the lag period to three and five
217 years. Finally, to assess potential heterogeneity associated with the use of cancer registries to

identify skin cancers in some sites, we repeated the analyses in these sites using the validated administrative data algorithm.

Pooling of Site-Specific Estimates

Site-specific estimates were pooled using DerSimonian and Laird random-effects meta-analysis.[31] Between-site heterogeneity was assessed using the I^2 statistic. Fixed-effects meta-analysis was used in a sensitivity analysis. All site-specific analyses and meta-analyses were conducted using SAS (with versions varying across sites).

RESULTS

HCTZ vs. ACEIs

The primary comparison included 511,115 initiators of HCTZ and 763,611 initiators of ACEIs (**Figure 1**). Patients were followed for a mean (standard error [SE]) of 5.5 (0.2) years, generating 6,671,299 person-years of follow-up. Baseline characteristics were well balanced between exposure groups after weighting (**Table 1** and **eTable 6**).

There was no overall association between HCTZ and the risk of keratinocyte carcinoma when compared with ACEIs (crude incidence rates: 796 vs. 768 per 100,000 person-years; HR: 1.02; 95% CI: 0.98-1.07; I^2: 73.4%) (**Table 2)**. In secondary analyses, cumulative durations of use of 5-10 years and ≥10 years were associated with an increased risk of keratinocyte carcinoma (HR: 1.09; 95% CI: 1.04-1.14 and HR: 1.12; 95% CI: 1.03-1.21, respectively) (**Table 3**). Similarly, higher cumulative doses generated elevated HRs (≥100,000 mg; HR: 1.49; 95% CI: 1.27-1.76). The cumulative incidence curves diverged around 13 years of follow-up (**Figure 2a**), and the estimated NNH was 1,494 and 843 patients at 5 and 10 years of follow-up, respectively. Finally, there was no evidence of effect measure modification by age, sex, or immunosuppressive status, and results remained consistent in sensitivity analyses, although the CIs excluded the null value using fixed-effects models (HR: 1.05; 95% CI: 1.03-1.07) (**Table 3**).

In sites with information on keratinocyte carcinoma subtypes, there was no overall increased risk for BCC or cSCC, although elevated HRs were observed with cumulative doses ≥100,000 mg for both subtypes, and among males for cSCC (**eTables 7** and **8**). Results remained consistent in other secondary and sensitivity analyses.

With respect to melanoma, HCTZ was not associated with an overall increased risk of melanoma compared with ACEIs (crude incidence rates: 66.2 vs. 59.2 per 100,000 person-years;

HR: 1.14; 95% CI: 0.99-1.31; I^2: 61.7%) (**Table 2**). Similarly, there was no clear evidence of duration or dose-response relations (**Table 3**). Overall, similar results were observed in subgroup analyses. The cumulative incidence curves diverged after around six years of follow-up (**Figure 2b**). The NNH were 1,911 and 895 patients at 5 and 10 years of follow-up, respectively. In sensitivity analyses, the on-treatment exposure definition led to an increase of melanoma (HR: 1.23; 95% CI: 1.03-1.45). The fixed-effects model generated a lower point estimate (HR: 1.08; 95% CI: 1.00-1.15). All other sensitivity analyses generated consistent results (**Table 3**).

HCTZ vs. CCBs

The secondary comparison included 539,854 initiators of HCTZ and 244,853 initiators of CCBs (**eFigure 1**). This cohort was followed for a mean (SE) of 5.7 (0.3) years, generating 5,026,778 person-years of follow-up. After weighting, baseline characteristics were well balanced between exposure groups (**eTable 9**).

Compared with CCBs, HCTZ was not associated with an overall increased risk of keratinocyte carcinoma (crude incidence rates: 847 vs. 802 per 100,000 person-years; HR: 1.08; 95% CI: 0.99-1.17; I^2: 85.2%) (**eTable 10**). Elevated HRs were observed with longer durations (≥10 years; HR: 1.34; 95% CI: 1.13-1.59) and higher cumulative doses (≥100,000 mg; HR: 1.59; 95% CI: 1.29-1.97) (**eTable 11**). The cumulative incidence curves diverged around eight years of follow-up (**eFigure 2a**). The NNH were 946 and 451 patients at 5 and 10 years of follow-up, respectively. Results remained consistent in other secondary and sensitivity analyses.

In analyses by keratinocyte carcinoma subtype, HCTZ was not associated with an increased risk of BCC or cSCC, although elevated HRs were observed with a cumulative dose

among males for cSCC (**eTables 12** and **13**). Other secondary and sensitivity analyses generated consistent results.

With respect to melanoma, HCTZ was associated with a 32% increased risk (crude incidence rates: 64.2 vs. 58.4 per 100,000 person-years; HR: 1.32; 95% CI: 1.19-1.46; I^2: 0%), with evidence of increased risks with longer durations and higher cumulative doses (**eTables 10** and **11**). The cumulative incidence curves diverged around two years of follow-up (**eFigure 2b**). The NNH were 1,627 and 966 patients at 5 and 10 years of follow-up, respectively. Results remained consistent across other secondary and sensitivity analyses, but with a decrease in the association using the modified outcome definition.

DISCUSSION

Our large, multi-site population-based cohort study indicate that while the use of HCTZ is not associated with an overall increased risk of keratinocyte carcinoma, longer durations and higher cumulative doses are associated with an increased risk when compared with ACEIs or CCBs. With respect to melanoma, HCTZ was associated with a 32% increased risk when compared with CCBs, but not ACEIs. This association increased with longer cumulative durations and higher cumulative doses. Overall, results remained relatively consistent across sensitivity analyses.

Our findings for keratinocyte carcinoma are consistent with previous studies reporting increased risk with longer durations and cumulative doses.[15,20,21] In contrast, findings for melanoma have been more heterogeneous, with some studies reporting an increased risk[8,14,19,20] and others no association.[10,11,16] However, several of these studies had methodological limitations which make their results difficult to interpret, such as comparing HCTZ users to non-users from the general population;[6-10,12,14,15,17,19-21] a comparator which may introduce confounding and detection bias (as HCTZ users are more likely to have increased contact with the healthcare system than non-users). There also is potential for time-window bias in prior case-control studies, as cases and controls were not matched on the disease duration.[6-8,10,12,14,17,19-21]

Our study has several strengths. First, the use of a new-user, active comparator design likely reduced potential confounding by indication and detection bias, while generating clinically-relevant results based on comparators for which there is clinical equipoise. Second, we compared HCTZ with two comparators (ACEIs and CCBs) given uncertainties regarding the potential photosensitizing effects of some antihypertensive drugs. Indeed, we observed some heterogeneity in the results with these two comparators, suggesting potential differences in their

photosensitizing effects. Third, we assembled large cohorts followed for up to 21 years allowing the statistical power and necessary follow-up time to assess the long-term safety of HCTZ. Lastly, pooling data from six Canadian provinces improved the generalizability of the results.

Our study has potential limitations. Due to its observational design, residual confounding due to unmeasured potential confounders (e.g., sun exposure, use of sunscreen, race or ethnicity, smoking status, and obesity) remains possible. However, these characteristics are unlikely to be differentially distributed between exposure groups. Second, exposure misclassification is possible as it was defined by prescription dispensations, which may not represent actual consumption. However, the on-treatment exposure definition in which patients were followed while continuously exposed yielded consistent results. Third, there is potential outcome misclassification for keratinocyte carcinoma and melanoma, as some sites identified these using cancer registries while others used a validated algorithm. Reassuringly, consistent results were obtained when using the algorithm in all sites. It was not possible to differentiate keratinocyte carcinoma into BCC and cSCC subtypes in all sites due to limitations in the precision of physician claims data. Finally, although we had a large sample size, some secondary analyses (e.g., patients with immunosuppressive conditions) were based on few exposed events, and thus should be interpreted with caution.

CONCLUSIONS

In this large multi-site population-based cohort study, while HCTZ was not associated with an overall increased risk of keratinocyte carcinoma when compared with ACEIs and CCBs, higher risks were observed with longer durations of use and higher cumulative doses. With respect to melanoma, HCTZ use was associated with an increased risk when compared with CCBs (but not ACEIs), which was further elevated with longer durations and higher cumulative

doses of HCTZ. Given the importance of HCTZ in the treatment of hypertension, physicians, patients, and decision-makers must weigh its benefits and risk compared with other antihypertensive drugs.

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Ministry of Health [publisher]. MOH (2019). Canadian Institute for Health Information [creator] (2019): Discharge Abstract Database (Hospital Separations). BC Ministry of Health [publisher]. MOH (2019); Canadian Institute for Health Information [creator] (2019): National Ambulatory Care Reporting System. BC Ministry of Health [publisher]. MOH (2019); BC Vital Statistics Agency [creator] (2019): Vital Statistics Deaths. BC Ministry of Health [publisher]. Vital Statistics Agency (2019). Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). The opinions, results, and conclusions reported are those of the authors. No endorsement by the provinces, data stewards, the Government of Alberta or Alberta Health, CIHI, Health Canada or CIHR is intended or should be inferred.

DISCLOSURES

Dr. Laurent Azoulay received speaker fees from Janssen, Pfizer, and Roche for work unrelated to this study. Dr. Robert Platt received consulting fees from Biogen, Boehringer Ingelheim, Merck, Nant Pharma, and Pfizer for work unrelated to this study. Dr. Wusiman Abibula conducted this research during his employment as Staff Scientist at the Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital prior to his employment at Complete HEOR Solutions. The remaining authors have no relevant conflicts of interest to disclose.

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FIGURE LEGENDS

Figure 1. Flowchart for the HCTZ vs. ACEIs study cohort construction (primary comparison)
Notes: (1) Numbers may not add up because site-specific cells with a value <6 were suppressed due to privacy restrictions. (2) Cancer registry data available in Manitoba and Saskatchewan (keratinocyte carcinoma and melanoma), and Ontario (melanoma only).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; HCTZ, hydrochlorothiazide; HIV, human immunodeficiency virus.

Figure 2. Pooled weighted cumulative incidence of keratinocyte carcinoma and melanoma among HCTZ users compared with ACEI users (primary comparison)
Notes: (1) Data truncated at 18 years of follow-up. (2) Cancer registry data available in Manitoba and Saskatchewan (keratinocyte carcinoma and melanoma), and Ontario (melanoma only)
Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; HCTZ, hydrochlorothiazide.

TABLES

Table 1. Baseline characteristics of new users of HCTZ and ACEIs (primary comparison)

	Unweighted*			Weighted†		
	HCTZ (n = 511,115)	**ACEIs (n = 763,611)**	**aSD**	**HCTZ**	**ACEIs**	**aSD**
Age (years)	66.3 ± 0.03	65.9 ± 0.02	0.03	66.3	66.7	0.09
Males	186,756 (36.5)	430,225 (56.3)	0.14	36.1	35.8	0.00
Calendar year at cohort entry						
1995-1999	92,235 (18.0)	100,952 (13.2)	0.07	17.5	17.4	0.00
2000-2004	168,088 (32.9)	220,741 (28.9)	0.03	39.1	39.1	0.00
2005-2009	138,624 (27.1)	176,075 (23.1)	0.04	26.5	26.6	0.00
2010-2014	84,919 (16.6)	169,486 (22.2)	0.06	13.1	13.1	0.00
2015-2018	27,249 (5.3)	96,357 (12.6)	0.15	3.8	3.8	0.00
Comorbidities‡						
Ischemic heart diseases	90,592 (17.7)	236,220 (30.9)	0.30	17.9	17.5	0.01
Cardiac dysrhythmias	54,920 (10.7)	113,842 (14.9)	0.12	10.6	10.7	0.00
Heart failure	10,084 (2.0)	44,309 (5.8)	0.20	2.0	1.9	0.00
Cerebrovascular diseases	32,751 (6.4)	78,341 (10.3)	0.13	6.5	6.7	0.01
Diabetes mellitus	54,087 (10.6)	242,954 (31.8)	0.55	10.3	10.4	0.00
Renal disease	7,868 (1.5)	21,808 (2.9)	0.09	1.5	1.5	0.01
Prescription drug use‡						
Antidiabetic drugs	14,942 (2.9)	160,279 (21.0)	0.58	2.8	2.9	0.00
Lipid-lowering drugs	65,639 (12.8)	260,289 (34.1)	0.50	12.5	12.1	0.01
Antithrombotic drugs	12,265 (2.4)	84,800 (11.1)	0.35	2.4	2.3	0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; aSD, absolute standardized difference; HCTZ, hydrochlorothiazide.

*Data are presented as n (%) or mean ± standard error.

†Baseline characteristics were weighted by both standardized morbidity ratio weights and the proportion of patients in each calendar year. Age as a continuous variable is only weighted by standardized morbidity ratio weights. Data are presented % or mean.

‡Comorbidities were assessed at any time before cohort entry. Prescription drug were assessed in the year before cohort entry.

Table 2. Hazard ratios for the association between the use of HCTZ and the risk of keratinocyte carcinoma and melanoma when compared with ACEIs, overall and by province (primary comparison)

	Keratinocyte carcinoma				Melanoma			
	No. of events	**Person-years**	**Crude incidence rate (95% CI)***	**HR (95% CI)†**	**No. of events**	**Person-years**	**Crude incidence rate (95% CI)***	**HR (95% CI)**
Overall								
HCTZ	24,734	2,763,441	796 (541-1,172)	1.02 (0.98-1.07)	2,020	2,763,441	66.2 (41.6-105.4)	1.14 (0.99-1.31)
ACEIs	36,440	3,907,858	768 (524-1,126)	Reference	2,689	3,907,858	59.2 (37.4-93.5)	Reference
Alberta								
HCTZ	2,171	231,761	937 (898-977)	1.02 (0.95-1.08)	213	231,761	91.9 (80.4-105.1)	0.93 (0.76-1.13)
ACEIs	3,080	336,537	915 (883-948)	Reference	328	336,537	97.5 (87.5-108.6)	Reference
British Columbia								
HCTZ	8,743	1,093,492	800 (783-816)	1.05 (1.02-1.09)	1,171	1,093,492	107.1 (101.1-113.4)	1.05 (0.95-1.15)
ACEIs	10,709	1,423,699	752 (738-767)	Reference	1,465	1,423,699	102.9 (97.8-108.3)	Reference
Manitoba‡								
HCTZ	2,045	367,838	556 (532-581)	1.01 (0.93-1.09)	133	367,838	36.2 (30.5-42.9)	1.50 (1.11-2.02)
ACEIs	2,202	427,831	515 (494-537)	Reference	114	427,831	27.0 (22.0-32.0)	Reference
Nova Scotia								
HCTZ	637	56,444	1,129 (1,044-1,220)	1.05 (0.91-1.21)	91	56,444	161.2 (131.3-198.0)	1.42 (0.98-2.06)
ACEIs	649	59,802	1,085 (1,005-1,172)	Reference	78	59,802	130.4 (104.5-162.8)	Reference
Ontario								
HCTZ	9,858	661,159	1,491 (1,462-1,521)	1.08 (1.05-1.11)	297	661,159	44.9 (40.1-50.3)	1.03 (0.88-1.21)
ACEIs	18,457	1,304,227	1,415 (1,395-1,436)	Reference	612	1,304,227	46.9 (43.4-50.8)	Reference
Saskatchewan‡								
HCTZ	1,280	352,746	363 (344-383)	0.88 (0.80-0.97)	115	352,746	32.6 (27.2-39.1)	1.51 (1.06-2.14)
ACEIs	1,343	355,762	377 (358-398)	Reference	92	355,762	25.9 (21.1-31.7)	Reference

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers; CI, confidence interval; HCTZ, hydrochlorothiazide; HR, hazard ratio.

*Per 100,000 person-years.

†Weighted by standardized morbidity ratio weights.

‡Cancer registry data available in Manitoba and Saskatchewan.

Table 3. Summary results for secondary and sensitivity analyses for the association between the use of HCTZ and the risk of keratinocyte carcinoma and melanoma when compared with ACEIs (primary comparison)

	HCTZ vs. ACEIs HR (95% CI)	
	Keratinocyte carcinoma	**Melanoma**
Main analysis	1.02 (0.98-1.07)	1.14 (0.99-1.31)
On-treatment approach	1.04 (0.98-1.09)	1.23 (1.03-1.45)
Cumulative duration		
<1 year	1.01 (0.93-1.11)	1.03 (0.91-1.16)
≥1 to <3 years	1.00 (0.97-1.04)	1.30 (1.04-1.63)
≥3 to <5 years	1.03 (0.95-1.12)	0.99 (0.76-1.29)
≥5 to <10 years	1.09 (1.04-1.14)	1.03 (0.86-1.22)
≥10 years	1.12 (1.03-1.21)	1.03 (0.64-1.64)
Time since initiation		
<3 years	1.02 (0.97-1.08)	1.22 (0.97-1.53)
≥3 to ≤5 years	1.04 (0.97-1.12)	0.96 (0.81-1.14)
>5 years	1.05 (1.00-1.10)	1.15 (0.94-1.42)
Cumulative dose		
<50,000 mg	1.01 (0.93-1.10)	1.15 (1.00-1.32)
≥50,000 to <100,000 mg	1.28 (0.91-1.79)	1.56 (0.98-2.48)
≥100,000 mg	1.49 (1.27-1.76)	1.73 (0.83-3.59)
Age[*]		
≤65 years	1.01 (0.89-1.15)	1.11 (0.94-1.30)
66-74 years	1.07 (1.04-1.09)	1.16 (0.99-1.36)
≥75 years	1.01 (0.93-1.10)	1.23 (0.87-1.73)
Sex		
Males	1.06 (1.01-1.11)	1.08 (0.98-1.20)
Females	1.02 (0.95-1.10)	1.19 (0.99-1.43)
Immunosuppressive status[†]		
Yes	1.21 (0.89-1.65)	1.36 (0.32-5.74)
No	1.02 (0.97-1.07)	1.15 (1.00-1.32)
IPCW	0.99 (0.90-1.09)	1.15 (1.01-1.31)
Extended lag period		
3 years	1.03 (0.99-1.08)	1.09 (0.94-1.27)
5 years	1.05 (1.00-1.09)	1.16 (0.96-1.40)
Modified outcome definition[#]	1.03 (0.98-1.08)	1.04 (0.95-1.13)
Fixed-effects models	1.05 (1.03-1.07)	1.08 (1.00-1.15)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; CI, confidence interval; HCTZ, hydrochlorothiazide; HR, hazard ratio; IPCW; inverse probability of censoring weighting.

[*]Alberta, Nova Scotia and Ontario not included in ≤65 years analysis.

[†]Immunosuppressive status defined as use of immunosuppressive drugs in the year before cohort entry.

[#]Outcomes defined using the algorithm definition in all sites (i.e., without cancer registry data).