Hypertension

ORIGINAL ARTICLE

Skin Cancer and Hydrochlorothiazide: Novel Population-Based Analyses Considering Personal Risk Factors Including Race/Ethnicity

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BACKGROUND: Hydrochlorothiazide, a common antihypertensive, has photosensitive properties, potentially increasing skin cancer risk. We evaluated melanoma and nonmelanoma skin cancer among hydrochlorothiazide users with 3 different cohorts as each allows assessment of different potential cofounders/effect modifiers, including race/ethnicity.

METHODS: We built 3 cohorts using IBM MarketScan Research Databases: Commercial and Encounters (>3.5 million individuals, 2010–2018), a subcohort with health risk assessment respondents (415, 330), and Medicaid (509, 767, 2011–2017). Adults (aged 18+ years) entered the respective cohort with a first-filled prescription (cohort entry) for hydrochlorothiazide (the exposure of interest) or angiotensin-converting enzyme (ACE) inhibitors (the active comparator), with ≥12 months of continuous enrollment with medical/pharmacy coverage at baseline. We excluded those who used hydrochlorothiazide/ACE inhibitor (including fixed-dose combination products) 12 months before cohort entry and those with prior skin cancer, HIV, or organ transplant. We compared the risk for hydrochlorothiazide versus ACE inhibitor using multivariate proportional hazards regression.

RESULTS: Baseline characteristics were similar, aside from more Black individuals among hydrochlorothiazide users (43.3% [95% CI, 43.0%–43.6%]) than ACE inhibitor users (28.1% [95% CI, 27.9%–28.3%]). The hazard ratio (95% CI) for nonmelanoma skin cancer related to hydrochlorothiazide (versus ACE inhibitor) was 0.96 (0.91–1.00) in the Commercial cohort, 1.01 (0.77–1.32) for the health risk assessment subcohort, and 1.33 (0.77–2.29) for Medicaid. For melanoma, the respective hazard ratios were 1.07 (0.95–1.20), 0.85 (0.43–1.67), and 0.93 (0.51–1.67), respectively.

CONCLUSIONS: Our evaluation using 3 different approaches, including adjustment for race/ethnicity, did not establish a clear difference between hydrochlorothiazide and ACE inhibitor in terms of skin cancer risk. ***(Hypertension.* 2023;80:2218–2225. DOI: 10.1161/HYPERTENSIONAHA.123.21274.)** • **Supplement Material**.

Key Words: antihypertensive agents ■ database ■ hydrochlorothiazide ■ melanoma ■ skin cancer

Hypertension, defined as systolic or diastolic blood pressure of ≥140/90 mm Hg, respectively, affects around 30% of adults worldwide.[1] Thiazide diuretics are recommended as first-line treatments, and hydrochlorothiazide is one of the most prescribed thiazide diuretics.[2,3] However, hydrochlorothiazide has photosensitive properties, potentially increasing skin damage and the risk of skin cancers in sun-exposed tissue.[4] Skin cancers are among the most common malignancies, and their incidence is rising,[5] making them a significant public health concern. Nonmelanoma skin cancer (NMSC) accounts for the vast majority of all skin cancer, with an incidence of 79.1 events per 100 000 individuals.[6] NMSC includes basal cell carcinoma (≈80% of all nonmelanoma skin cancer), squamous cell carcinoma (≈20%), and others (<1%).[7] Although less frequent (3.6 per 100 000) than nonmelanoma skin cancer, melanoma has much higher

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.123.21274.
For Sources of Funding and Disclosures, see page 2224.

Hypertension is available at www.ahajournals.org/journal/hyp

NOVELTY AND RELEVANCE

What Is New?

Although many studies have shown an increased risk of skin cancer among hydrochlorothiazide, the results are still conflicting. Not all studies control for race/ethnicity.

We used different cohorts of hydrochlorothiazide users to minimize bias of individual characteristics and account for different risk factors and potential confounders, including race/ethnicity.

What Is Relevant?

Hydrochlorothiazide, one of the most commonly prescribed antihypertensives, has photosensitivity properties that potentially increase skin cancer risk.

Black individuals may have different patterns of hydrochlorothiazide use compared with non-Black individuals and may have different skin cancer risk profiles.

Clinical/Pathological Implications?

Hydrochlorothiazide could increase the risk of skin cancer, although we did not observe a clear difference in skin cancer risk among hydrochlorothiazide and angiotensin-converting enzyme (ACE) inhibitor users, even when controlling for race/ethnicity.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
CI	confidence interval
HRA	health risk assessment
ICD	International Classification of Diseases
IQR	interquartile range
NMSC	nonmelanoma skin cancer

mortality,[6] with the 5-year survival for advanced melanoma being <20%.

There is a steady interest in potential links between skin cancer and hydrochlorothiazide.[4,8–12] The International Agency for Research on Cancer classified hydrochlorothiazide as a group 2B drug, that is, possibly carcinogenic.[13] Interest is fueled by conflicting conclusions in the literature, with some observational studies and meta-analyses reporting associations[8,12,14–20] but not others.[11,12,21–23] Various reasons could explain the conflicting findings, including the selected study population and available information in each dataset.

Observational studies are prone to bias that can be difficult to mitigate or control. A triangulation framework, that is, the combination of several different approaches to evaluate the same association, could likely account for different unrelated sources of bias in each approach[24,25] and provide a fresh perspective. Thus, we evaluated skin cancer (melanoma and nonmelanoma skin cancer) in 3 of the largest population-based cohorts of persons exposed to antihypertensives, including hydrochlorothiazide. Moreover, our analyses included a focus on factors not typically considered in pharmacoepidemiology, including race/ethnicity and personal skin cancer risk factors.

METHODS

Data Availability

IBM MarketScan Research Databases is not in the public domain but is available to researchers at a cost. Data were used in compliance with privacy and confidentiality requirements. We used IBM MarketScan Research Databases that contain de-identified patient-level claims data on in-hospital and outpatient resources used by patients from the United States (including medical appointments and services, emergency room visits, hospital stays, and drug dispensation). We performed separate analyses within Commercial Claims and Encounters, which includes data from people insured by employer-sponsored plans (≈48% of the US population) and the Medicaid database, which includes individuals covered by Medicaid programs that comprises mainly low-income Americans (in 2018, 97 million people).[26,27]

Study Population

We studied individuals enrolled in Commercial plans from 2010 to 2018 and Medicaid care from 2011 to 2017. Adults (aged 18+ years) entered the respective cohort with their first-filled prescription (cohort entry) for hydrochlorothiazide (the exposure of interest) angiotensin-converting enzyme (ACE) inhibitors, the comparator. Inclusion criteria also required ≥12 months of continuous enrollment with medical/pharmacy coverage before cohort entry. We excluded individuals (1) with previous hydrochlorothiazide/ACE inhibitor use (including fixed-dose combinations) 12 months before the first prescription, or (2) prescribed both hydrochlorothiazide and ACE inhibitor, or (3) with a diagnosis of the outcome (NMSC or melanoma) any time before cohort entry, or (4) with HIV infection or solid organ transplant (who likely have different risk profiles for skin cancer compared with the general population). We also formed a subcohort from the Commercial Claims database of individuals with at least 1 health risk assessment (HRA) questionnaire at any time before cohort entry. The HRA is linked to a subsample of the MarketScan Commercial Claims-based population,

providing biometrics such as height and weight for body mass index calculation and self-reported health risk indicators such as smoking. These data are collected annually as part of corporate health programs; participation is voluntary, but the HRA has been validated as a reliable source of self-reported information.[28] In this third cohort, we used HRA data to assess additional cancer risk factors, including physical activity, smoking, unhealthy weight, and alcohol, as these daily lifestyle factors are associated with skin cancer.[29] These 3 cohorts represented our triangulation framework, with different strengths and limitations, as they provide information on 2 different populations in terms of sociodemographic characteristics, and each one allows assessment of different potential cofounders/effect modifiers.

Treatment Exposure

We compared hydrochlorothiazide and ACE inhibitor users. By using active comparators, we were able to compare relevant therapeutic options used in the real world while mitigating bias and avoiding unmeasured confounders by restricting our analyses to people who presumably had similar treatment indications. Drug exposures were identified within dispensation records using the National Drug Code. Person-time after the switch was censored for any patient on an antihypertensive of interest who later switched to another antihypertensive of interest (including fixed-dose combination antihypertensives).

Outcomes

NMSC was defined by *International Classification of Diseases (ICD)* inpatient and outpatient diagnostic codes (*ICD-9* codes 173.0-173.9, 232 [any], *ICD-10* code C44 [any]) linked to Current Procedural Terminology codes (11600-11606, 11620-11626, 11640-11646, 17260-17266, 17270-17276, 17280-17286, 17311-17315).[7,30,31] Melanoma was defined by *ICD-9* diagnostic code 172 (any) or *ICD-10* diagnostic code C43 (any) in hospital records or outpatient physician visits.[32,33] Our primary analyses applied a lag time of 1 year following the first prescription to account for the time between exposure to a carcinogen and cancer development (ie, events happening within the first year of hydrochlorothiazide/ACE inhibitor treatment did not count as outcomes). As the true plausible induction time is unknown, we performed 2 preplanned sensitivity analyses using 6 months and 2 years of lag time (Supplemental Material).

Covariates

Baseline data (at cohort entry) included age, biological sex, place of residence (rural versus urban), region of residence (northeast, north central, south, west), and calendar year. Clinical conditions (that might affect exposure and outcome) included the Charlson Comorbidity Index, diabetes, chronic kidney disease and outpatient dialysis, autoimmune disease, and disease duration (years)—all at any time before cohort entry. We also included prior antihypertensives and other drugs that might be confounders or effect modifiers in our analyses due to photosensitizing properties (macrolides, methoxypsoralen, voriconazole, retinoids, aminoquinolines, tetracyclines, quinolones, amiodarone, quinidine, aspirin, non-steroidal anti-inflammatory drugs, statins) or to their associations with skin cancer (corticosteroids and other immunosuppressants).[20,34] Race/ethnicity was only available in the Medicaid database. With the HRA subcohort, we selected other potential confounders: physical activity, smoking, unhealthy weight (body mass index >25 for either biological sex or waist circumference ≥40 inches for males and ≥35 inches for females), and alcohol consumption.[29] Since participants completed the questionnaire at different times in the HRA subset, we also adjusted for the time from the HRA questionnaire to the first prescription of a drug of interest.

Statistical Analysis

All analyses were done using Statistical Analysis System version 9.4 (SAS Institute, Inc). We described baseline characteristics using frequency/percentages for categorical variables, and mean/SD or median/interquartile range (IQR) for continuous variables.

As noted earlier, we analyzed person-time starting 1 year after the first prescription and continuing until the outcome (NMSC or melanoma, as separate outcomes), hydrochlorothiazide/ACE inhibitor discontinuation (>30 days gap between prescriptions), switch to a new antihypertensive or addition of another antihypertensive, end of the study period (December 31, 2018), loss of health/drug insurance coverage, or death, whichever occurred first. Multivariable Cox proportional hazards regression was used to examine associations between the first occurrence of interest (NMSC or melanoma, in separate models) and the principal exposure of interest (hydrochlorothiazide versus ACE inhibitor). All models were adjusted for the covariates described

	NMSC cohort	Melanoma cohort
Initial cohort	**Commercial, n=8,658,599 Medicaid, n=998,008**	
Exclusions		
Aged <18 years	Commercial, n=32,114 Medicaid, n=25,077	
Previous use of HCTZ/ACEI	Commercial, n=2,231,916 Medicaid, n=173,200	
<12 months of insurance	Commercial, n=3,929,684 Medicaid, n=502,898	
Prior NMSC, HIV or solid transplant	Commercial, n=712,272 Medicaid, n=681,711	-
Prior melanoma, HIV or solid transplant	-	Commercial, n=41,922 Medicaid, n=41,977
Final cohort (remained individuals)		
Commercial	**1,752,613**	**1,783,174**
Commercial sub-cohort	**205,521**	**209,809**
Medicaid	**254,911**	**254,856**

Figure. Cohort selection.
ACEI indicates angiotensin-converting enzyme; HCTZ, hydrochlorothiazide; and NMSC, nonmelanoma skin cancer.

Table 1. Baseline Characteristics of Included Individuals

	Commercial		Commercial HRA		Medicaid	
	NMSC	Melanoma	NMSC	Melanoma	NMSC	Melanoma
Characteristics	N=1 752 613	N=1 783 174	N=205 521	N=209 809	N=254 911	N=254 856
Age, mean (SD)	49.1 (9.8)	49.3 (9.7)	48.3 (9.2)	48.5 (9.2)	44.9 (12.5)	44.9 (12.5)
CCI, mean (SD)	0.3 (0.7)	0.3 (0.7)	0.3 (0.6)	0.3 (0.6)	0.4 (0.9)	0.4 (1.0)
Biological female sex, n (%)	892 641 (50.9)	906 061 (50.8)	103 634 (50.4)	105 403 (50.2)	164 704 (64.6)	164 643 (64.6)
Urban area, n (%)	1 461 332 (83.4)	1 486 948 (83.4)	173 912 (84.6)	177 607 (84.7)	…	…
Region, n (%)						
North Central	369 687 (21.1)	374 987 (21.0)	49 565 (24.1)	50 365 (24.0)	…	…
Northeast	277 387 (15.8)	281 034 (15.8)	20 814 (10.1)	21 202 (10.1)	…	…
South	835 388 (47.7)	852 154 (47.8)	109 709 (53.4)	112 191 (53.5)	…	…
West	255 904 (14.6)	260 560 (14.6)	25 372 (12.3)	25 989 (12.4)	…	…
Unknown	14 247 (0.8)	14 439 (0.8)	61 (0)	62 (0)	…	…
Year of cohort entry, n (%)						
2011	405 394 (23.1)	410 222 (23.0)	18 479 (9.0)	18 713 (8.9)	…	…
2012	319 325 (18.2)	324 028 (18.2)	27 301 (13.3)	27 712 (13.2)	…	…
2013	239 521 (13.7)	243 673 (13.7)	27 648 (13.5)	28 107 (13.4)	51 224 (20.1)	51 229 (20.1)
2014	186 252 (10.6)	190 048 (10.7)	29 604 (14.4)	30 204 (14.4)	41 319 (16.2)	41 298 (16.2)
2015	177 981 (10.2)	181 795 (10.2)	30 306 (14.7)	30 986 (14.8)	46 832 (18.4)	46 820 (18.4)
2016	157 344 (9.0)	160 696 (9.0)	29 271 (14.2)	29 933 (14.3)	45 745 (17.9)	45 747 (18.0)
2017	130 682 (7.5)	133 523 (7.5)	22 909 (11.1)	23 545 (11.2)	36 531 (14.3)	36 500 (14.3)
2018	136 114 (7.8)	139 189 (7.8)	20 003 (9.7)	20 609 (9.8)	33 260 (13.0)	33 262 (13.1)
CCI>1, n (%)	381 746 (21.8)	390 433 (21.9)	43 793 (21.3)	45 100 (21.5)	62 736 (24.6)	62 796 (24.6)
Diabetes, n (%)	382 485 (21.8)	387 687 (21.7)	41 913 (20.4)	42 596 (20.3)	70 194 (27.5)	70 201 (27.5)
Chronic kidney disease, n (%)	10 669 (0.6)	10 909 (0.6)	1293 (0.6)	1336 (0.6)	3572 (1.4)	3570 (1.4)
Autoimmune diseases, n (%)	98 667 (5.6)	101 380 (5.7)	12 346 (6.0)	12 758 (6.1)	7055 (2.8)	7060 (2.8)
Hypertension, n (%)	1 195 384 (68.2)	121 8185 (68.3)	137 149 (66.7)	140 340 (66.9)	87 533 (34.3)	87 621 (34.4)
Outpatient chronic dialysis, n (%)	2169 (0.1)	2199 (0.1)	126 (0.1)	127 (0.1)	872 (0.3)	869 (0.3)
Drugs with photosensitizing effect, n (%)	916 148 (52.3)	935 436 (52.5)	125 472 (61.1)	128 514 (61.3)	141 943 (55.7)	141 905 (55.7)
Other relevant drugs, n (%)	1 008 235 (57.5)	1 028 368 (57.7)	128 762 (62.7)	131 763 (62.8)	187 154 (73.4)	187 110 (73.4)
Other antihypertensive drugs, n (%)	628 982 (35.9)	641 083 (36.0)	72 183 (35.1)	73 875 (35.2)	122 644 (48.1)	122 627 (48.1)
Physical activity, n (%)						
Active level	…	…	8018 (3.9)	8250 (3.9)	…	…
Moderate level	…	…	5224 (2.5)	5373 (2.6)	…	…
Non or light exerciser	…	…	180 869 (88.0)	184 443 (87.9)	……	…
Missing	…	…	11 410 (5.6)	11 743 (5.6)	…	…
Health risk for weght, n (%)						
Missing	…	…	88 878 (43.2)	91 100 (43.4)	…	…
No	…	…	18 791 (9.1)	19 305 (9.2)	…	…
Yes	…	…	97 852 (47.6)	99 404 (47.4)	…	…
Smoking status, n (%)						
Current smoker	…	…	17 086 (8.3)	17 389 (8.3)	…	…
Never smoked	…	…	166 307 (80.9)	169 819 (80.9)	…	…
Past smoker	…	…	22 128 (10.8)	22 601 (10.8)	…	…
Use of alcohol, n (%)						
Heavy use	…	…	4266 (2.1)	4361 (2.1)	…	…
Moderate use	…	…	2071 (1.0)	2130 (1.0)	…	…
No use/rare	…	…	110 176 (53.6)	112 310 (53.5)	…	…
Missing	…	…	89 008 (43.3)	91 008 (43.4)	…	…

(*Continued*)

Table 1. Continued

Characteristics	Commercial		Commercial HRA		Medicaid	
	NMSC	Melanoma	NMSC	Melanoma	NMSC	Melanoma
	N=1 752 613	N=1 783 174	N=205 521	N=209 809	N=254 911	N=254 856
Race/ethnicity, n (%)						
Black	…	…	…	…	87 632 (34.4)	87 604 (34.4)
Hispanic	…	…	…	…	4123 (1.6)	4125 (1.6)
Other	…	…	…	…	29 547 (11.6)	29 539 (11.6)
White	…	…	…	…	124 121 (48.7)	124 098 (48.7)
Missing	…	…	…	…	9488 (3.7)	9490 (3.7)

CCI indicates Charlson Comorbidity Index; HRA, health risk assessment questionnaire; and NSMC, nonmelanoma skin cancer.

in the previous section, and results are expressed as hazard ratio with 95% confidence interval (CI). We performed preplanned sensitivity analysis (Supplemental Material): (1) to test different lag periods (6 months and 2 years), as abovementioned and (2) restricting the population to those with a hypertensive diagnosis, defined as 1 physician outpatient billing claim or 1 hospital discharge with a primary or secondary diagnosis of hypertension—*ICD-9* code 401.xx-405.xx, or *ICD-10*: I10.x-I15.x), any time before or 1 month after the first prescription of drugs of interest.

Ethics Approval

We followed local laws and regulations for de-identified data, and the study was approved by McGill University Research Ethics Office (Institutional Review Board; patients' informed consent was not applicable).

RESULTS

We studied over 3.5 million individuals in the Commercial Claims cohorts, 415 330 in the HRA subcohort, and 509 767 in the Medicaid cohorts (Figure). Median follow-up was 10 years (IQR, 5–25) for NMSC and 10 years (IQR, 5–24) for melanoma for the Commercial Claims cohorts, 10 years (IQR, 5–28) and 11 years (IQR, 5–29) for the HRA subcohorts, and 8 years (IQR, 5–18) and 8 years (IQR, 5–28) for Medicaid cohorts, respectively.

Baseline characteristics are presented in Table 1. Medicaid individuals were more often females and tended to be younger than the Commercial Claims individuals. In all cohorts, the age distribution was similar among treatments (hydrochlorothiazide and ACE inhibitor), but hydrochlorothiazide users were more likely to be female than ACE inhibitor users. In Medicaid data, we noticed a trend for more Black individuals among hydrochlorothiazide users (43.3% [95% CI, 43.0%–43.6%]) than ACE inhibitor users (28.1% [95% CI, 27.9%–28.3%]). Other baseline characteristics were similar between treatment groups (Tables S1 through S3).

Skin cancer incidence rates were similar among exposure groups. In all 3 cohorts (Commercial Claims, HRA, and Medicaid), we did not observe clear differences in NMSC risk between individuals exposed to hydrochlorothiazide versus ACE inhibitor. We also were unable to demonstrate clear differences in melanoma risk between hydrochlorothiazide versus ACE inhibitor in all cohorts (Table 2).

Results remained similar (no clear association between hydrochlorothiazide and skin cancer) when varying the lag period for 6 months and 2 years (Tables S4 and S5, respectively) or restricting the analysis to individuals with hypertension diagnosis (Table S6).

DISCUSSION

In this triangulation analysis, we were unable to demonstrate a clear difference in NMSC or melanoma risk comparing hydrochlorothiazide and ACE inhibitor using 3 different cohorts.

Race/ethnicity is an important risk factor contributing to skin cancer incidence. In our Medicaid analyses (where we could control for race/ethnicity), we noted a trend for more Black hydrochlorothiazide users than Black ACE inhibitor users (43% versus 29%), which likely reflects the promotion of thiazide diuretics as first-line agents in Black individuals due to their high effectiveness in this group compared with ACE inhibitor.[35] Since Black people are at a lower risk of skin cancer, not adjusting for race/ethnicity could mask an increased risk of skin cancer due to hydrochlorothiazide if it truly existed.[11] In a recent US study, hydrochlorothiazide (versus ACE inhibitor) use was associated, only with White people, with slightly higher risks of subtypes of NMSC, basal cell cancer (HR, 1.09 [95% CI, 1.07–1.11]) and squamous cell cancer (HR, 1.15 [95% CI, 1.12–1.17]).[14]

Other personal risk factors are potential confounders of relationships between antihypertensive medications and skin cancer. For instance, smoking is a well-known factor in cancer development, including skin cancer.[36,37] It can affect blood pressure,[38] potentially leading to different patterns of antihypertensive drug use in smokers. We did not demonstrate an increased skin cancer risk with hydrochlorothiazide versus ACE inhibitor in analyses adjusted for smoking and other personal factors

Table 2. Unadjusted and Adjusted HRs for Skin Cancer, Nonmelanoma, and Melanoma

Exposure	No. events	Rate/100 PY (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
NMSC				
Commercial claims				
ACEI	4929	0.71 (0.69–0.73)	Ref	Ref
HCTZ	3220	0.67 (0.65–0.70)	0.95 (0.91–0.99)	0.96 (0.91–1.00)*
Commercial claims+HRA				
ACEI	707	0.75 (0.70–0.81)	Ref	Ref
HCTZ	416	0.63 (0.58–0.70)	0.85 (0.75–0.96)	1.01 (0.77–1.32)†
Medicaid data				
ACEI	45	0.05 (0.04–0.07)	Ref	Ref
HCTZ	23	0.05 (0.03–0.07)	0.95 (0.57–1.57)	1.33 (0.77–2.29)‡
Melanoma				
Commercial claims				
ACEI	760	0.11 (0.10–0.11)	Ref	Ref
HCTZ	553	0.11 (0.10–0.12)	1.06 (0.95–1.18)	1.07 (0.95–1.20)*
Commercial claims+HRA				
ACEI	109	0.11 (0.09–0.14)	Ref	Ref
HCTZ	63	0.09 (0.07–0.12)	0.84 (0.62–1.15)	0.85 (0.43–1.67)†
Medicaid data				
ACEI	41	0.05 (0.03–0.06)	Ref	Ref
HCTZ	17	0.03 (0.02–0.06)	0.75 (0.42–1.32)	0.93 (0.51–1.67)‡

ACEI indicates angiotensin-converting enzyme inhibitor; HCTZ, hydrochlorothiazide; HR, hazard ratio; HRA, health risk assessment questionnaire; NSMC, nonmelanoma skin cancer; and PY, person-year.

*Model adjusted for age, biological sex, urban vs rural residence, region of residence, calendar year, comorbidities, baseline use of other therapies with potential photosensitizing properties and immunosuppressant effects, baseline use of other relevant drugs including other antihypertensive drugs.

†Model adjusted for all variables listed in a and additionally for smoking status, health risk for weight, use of alcohol, physical activity, and time from health risk assessment questionnaire to first prescription of a drug of interest.

‡Model adjusted for age, biological sex, race/ethnicity, calendar year, comorbidities, baseline use of other therapies with potential photosensitizing properties and/or immunosuppressant effects, baseline use of other relevant drugs including other antihypertensive drugs.

using the Commercial HRA subcohort. However, the smaller size of this cohort created limits in our estimates' precision.

At least 1 study established a biological plausibility between hydrochlorothiazide use and skin cancer since human skin cancer undergoes precancerous changes when chronically exposed to both UVA and hydrochlorothiazide.[4] Studies of hydrochlorothiazide in Australia[8] and the United States[14–20] suggested an increased risk of NMSC and, in some, melanoma risk.[8,12,15] Limitations to consider within these studies include an important proportion of White populations who are naturally at greater risk of skin cancer and concomitant use of other photosensitizing agents with hydrochlorothiazide, such as amiloride. On the other hand, several studies showed no association or limited evidence between hydrochlorothiazide and skin cancer; this could be explained by the lack of differentiation of cancer subtypes, limited follow-up, cultural differences in sun exposure (eg, use of sunscreen and hats), and various potential unmeasured residual confounding.[11,12,21–23] Other diuretics commonly used to treat hypertension and cardiovascular disease may carry photosensitizing properties, but evidence of skin cancer risk is still conflicting.[10,39] Indapamide was found to be associated with skin cancer, particularly melanoma,[10,39,40] but not in all studies;[39,41] contrasting findings were also observed for chlortalidone, amiloride, bumetanide, and furosemide.[10,39–44] Although, in general, the evidence does not show a greater risk of skin cancer, future studies could address the use of other diuretics, alone or in combination, with skin cancer risk.

An important strength of our study is using a new data source (especially the HRA subcohort) that was not previously explored for associations between antihypertensives and skin cancer risk. However, since cancer is a relatively uncommon outcome, some of our estimates lacked precision, especially for subset analyses. Our study did not clearly show a higher skin cancer risk for hydrochlorothiazide compared with ACE inhibitor, though it should be remembered that ACE inhibitor may also have a potential role in skin cancer risk.[15,42,45] Moreover, hydrochlorothiazide is frequently used in combination with other antihypertensives, but our results do not inform discussions of risk in that setting. Residual confounders remain (eg, race for the Commercial database), but our triangulation approach was an effort to mitigate this bias.

In conclusion, our triangulating attempts to evaluate skin cancer risk considering 3 different approaches, including adjustment for race/ethnicity, did not establish a clear difference between hydrochlorothiazide and ACE inhibitor in the real world.

PERSPECTIVES

Since the first suggestion of skin cancer risk in hydrochlorothiazide users, there have been a few conflicting studies, with some showing increased risk but not all. Most studies were represented by White users, who are at higher risk of skin cancer. Many studies could not account for confounders like race/ethnicity, imposing an important limitation. In our study, we observed that Black individuals were more exposed to hydrochlorothiazide than White individuals, suggesting a different treatment pattern between the 2 populations and likely reflecting

the promotion of thiazide diuretics for Black individuals. Given the large number of chronic hydrochlorothiazide users, the possible association with skin cancer can pose individual and public health consequences. Understanding what factors potentially increase the risk of cancer helps support informed decision-making and elaborate appropriate risk mitigation strategies.

Nonetheless, hydrochlorothiazide has effectively controlled hypertension and avoided cardiovascular events and mortality. Thus, the risk-benefit of using hydrochlorothiazide as an effective treatment and its safety issues on cancer development should be addressed carefully. Our triangulation approach did not find a significant difference in skin cancer among hydrochlorothiazide and ACE inhibitor users when adjusting for risk factors, such as race/ethnicity. However, as a relatively uncommon cancer, many of our estimates might lack precision.

ARTICLE INFORMATION

Received March 28, 2023; accepted July 10, 2023.

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Sources of Funding

This work was supported by the Canadian Institutes of Health Research (TD3-137716 and DMC-166262).

Disclosures

None.

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