Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark

Sidsel Arnspang Pedersen, MD,[a,b,c] David Gaist, PhD,[a,b] Sigrun Alba Johannesdottir Schmidt, PhD,[d] Lisbet Rosenkrantz Hölmich, DMSc,[e] Søren Friis, MD,[d,f,g] and Anton Pottegård, PhD[c]
Odense, Aarhus, Herlev, and Copenhagen, Denmark

Background: Hydrochlorothiazide, one of the most frequently used diuretic and antihypertensive drugs in the United States and Western Europe, is photosensitizing and has previously been linked to lip cancer.

Objective: To examine the association between hydrochlorothiazide use and the risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Methods: From the Danish Cancer Registry, we identified patients (cases) with nonmelanoma skin cancer (NMSC) during 2004-2012. Controls were matched 1:20 by age and sex. Cumulative hydrochlorothiazide use (in 1995-2012) was assessed from the Danish Prescription Registry. Using conditional logistic regression, we calculated odds ratios (ORs) for BCC and SCC associated with hydrochlorothiazide use.

Results: High use of hydrochlorothiazide (≥50,000 mg) was associated with ORs of 1.29 (95% confidence interval [CI], 1.23-1.35) for BCC and 3.98 (95% CI, 3.68-4.31) for SCC. We found clear dose-response relationships between hydrochlorothiazide use and both BCC and SCC; the highest cumulative dose category (≥200,000 mg of HCTZ) had ORs of 1.54 (95% CI, 1.38-1.71) and 7.38 (95% CI, 6.32-8.60) for BCC and SCC, respectively. Use of other diuretics and antihypertensives was not associated with NMSC.

Limitations: No data on sun exposure were available.

Conclusions: Hydrochlorothiazide use is associated with a substantially increased risk of NMSC, especially SCC. (J Am Acad Dermatol 2018;78:673-81.)

Key words: antihypertensives; cancer risk; hydrochlorothiazide; nonmelanoma skin cancer; pharmacoepidemiology; pharmacology; skin cancer.

From the Department of Neurology, Odense University Hospital[a]; Department of Clinical Research, Faculty of Health Sciences,[b] Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense[c]; Department of Clinical Epidemiology, Aarhus University Hospital[d]; Department of Plastic Surgery, Herlev-Gentofte Hospital[e]; Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen[f]; and Department of Public Health, University of Copenhagen.[g]

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Correspondence to: Anton Pottegård, PhD, Clinical Pharmacology and Pharmacy, University of Southern Denmark, JB Winsløwsvej 19, 2, 5000 Odense C, Denmark. E-mail: apottegaard@health.sdu.dk.

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Nonmelanoma skin cancer (NMSC) is the most common cancer in humans, and the incidence is increasing, particularly among the elderly.[1] Exposure to ultraviolet (UV) light and a UV-susceptible skin phenotype have been established as important risk factors for NMSC. In addition, the use of immunosuppressants (eg, cyclosporine and azathioprine) induces NMSC, and other drugs have been suggested to either increase (eg, topical and systemic calcineurin inhibitors) or decrease (eg, aspirin and other nonsteroidal anti-inflammatory drugs) the risk of NMSC.[2-5]

CAPSULE SUMMARY

- Hydrochlorothiazide is photosensitizing and has been linked to lip cancer.
- We found a dose-dependent increased risk of nonmelanoma skin cancer, particularly squamous cell carcinoma, among users of hydrochlorothiazide.
- Hydrochlorothiazide use should be carefully considered because of its association with nonmelanoma skin cancer.

Recently, we reported a strong association between use of the diuretic hydrochlorothiazide (HCTZ) and squamous cell carcinoma (SCC) of the lip.[6] We found a clear dose-response pattern, with an estimated 7-fold increased risk of SCC lip cancer with cumulative use of 100,000 mg or more of HCTZ. Our findings were in line with the results of previous studies from the United States[7] and the recent classification of HCTZ as possibly carcinogenic to humans (group 2B) by the International Agency for Research on Cancer.[8] As HCTZ is among the most widely used drugs in the United States and Western Europe,[9] a carcinogenic effect of HCTZ would have a considerable impact on public health.

Few studies have investigated the association between thiazide use and NMSC risk.[10-13] Although the study results have been inconsistent, they indicate that HCTZ use increases the risk of NMSC. Some of the inconsistencies may derive from difficulties in disentangling the effect of HCTZ from that of other antihypertensives, as HCTZ is mainly prescribed in combination with other diuretics (primarily amiloride) or nondiuretic antihypertensives.[10-13] Therefore, we were interested in examining the association between HCTZ use and NMSC risk more extensively and evaluating the individual effect of HCTZ.[6] Specifically, we used detailed data from the Danish demographic, prescription, and disease registries to examine the association between HCTZ use and the risk of basal cell carcinoma (BCC) or SCC of the skin.

METHODS

We performed a nested case-control analysis based on nationwide registry data. We compared HCTZ use among persons in whom SCC and BCC of the skin had been diagnosed with that of cancer-free population controls and estimated odds ratios (ORs) for SCC and BCC associated with previous HCTZ use.

Data sources

We obtained data from 5 nationwide data sources: the Danish Cancer Registry,[14] the National Prescription Registry,[15] the National Patient Registry,[16] the Danish Education Registers,[17] and the Danish Civil Registration System.[18] We linked all data sources using the unique civil registration number assigned to all Danish residents. Details of codes used to define drug exposure and covariates have been provided elsewhere.[6]

Selection of patients with NMSC

The patients with NMSC were Danish residents with histologic verification of their first diagnosis of SCC or BCC of the skin between January 1, 2004, and December 31, 2012. We excluded patients with SCC of the lip, as they were evaluated in our previous study.[6] We required patients to have no previous skin or other cancer diagnoses before the first diagnosis of BCC or SCC (index date) and to have resided in Denmark for at least 10 consecutive years before the index date. We also required patients to have no record of organ transplantation; HIV diagnosis; or use of azathioprine, cyclosporine, or mycophenolate mofetil, as immunosuppressive disease and therapy may predispose to skin cancer.[2,19] We defined the date of the first skin cancer diagnosis as the index date.

Population controls

Controls were selected by risk-set sampling. For each case, we matched 20 population controls by sex and birth year, applying the same selection criteria as for cases. Controls were allotted the index dates of their corresponding cases. As individuals were eligible to be controls before they became case patients, the calculated ORs provide unbiased estimates of the incidence rate ratios that would have emerged from a cohort study based on the source population.

Definition of exposure

On the basis of prescription data from 1995 onward, ever use of HCTZ was defined as having filled 1 or more prescriptions for an

Abbreviations used:

BCC: basal cell carcinoma
CI: confidence interval
HCTZ: hydrochlorothiazide
NMSC: nonmelanoma skin cancer
OR: odds ratio
SCC: squamous cell carcinoma
UV: ultraviolet

HCTZ-containing drug before the index date and never use as no HCTZ-containing prescription. In Denmark, HCTZ is prescribed almost exclusively as a part of combination preparations with potassium-sparing diuretic amiloride or nondiuretic antihypertensives, predominantly angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists. The content of HCTZ was identified in all combination or single drugs dispensed to individuals in the study population, and on the basis of this information the cumulative dose of HCTZ to which each individual had been exposed up to index date was calculated. High use of HCTZ was defined as filled prescriptions equivalent to 50,000 mg or more of HCTZ, corresponding to 2000 or more defined daily doses (ie, ~6 years of cumulative use). Prescriptions filled within 2 years before the index date (lag time) were disregarded, primarily to allow a reasonable induction period for an effect on BCC or SCC risk and to guard against the possibility that medical attention before the skin cancer diagnosis had influenced the decision to prescribe HCTZ.[20]

Other variables

We defined potential confounders on the basis of the following data: (1) use of selected drugs with suggested photosensitizing properties, including oral retinoids, topical retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene[10,13,21,22]; (2) use of drugs with suggested antineoplastic effects, including aspirin, nonsteroidal anti-inflammatory drugs, and statins[3]; (3) composite measures of hospital diagnoses and disease-specific drugs defining medical histories of diabetes, chronic obstructive pulmonary disease, chronic renal insufficiency, or conditions associated with heavy alcohol consumption (see the Supplemental and Sensitivity Analyses; available at http://www.jaad.org); (4) Charlson comorbidity index scores (0, low; 1-2, medium; or ≥3, high) derived from the prevalence of 19 chronic conditions; and (5) highest achieved education (basic, medium, higher, or unknown). Exposure to each potential confounder drug was defined as 2 or more prescriptions on separate dates, and the hospital history of each of the selected medical conditions was defined as a primary or secondary discharge or outpatient diagnosis. For all covariates, we disregarded information within 2 years before the index date.

Analyses

All analyses followed a conventional matched case-control approach. We computed the frequency and proportion of cases and controls within categories of the exposure and covariates. We used conditional logistic regression analysis to compute ORs with 95% confidence intervals (CIs) for the association of BCC or SCC with HCTZ use adjusted for the predefined potential confounders. In addition, to examine potential dose-response relationships, we stratified analyses according to predefined categories of cumulative HCTZ use. The statistical significance of the dose-response pattern was assessed by restriction to HCTZ ever users and estimation of the incremental OR for each 10,000 mg of HCTZ by using ordinary logistic regression while also adjusting for sex and age as a continuous variable. In all analyses, BCC and SCC were analyzed separately, and those with never use of HCTZ served as the reference group unless stated otherwise. We performed a number of preplanned supplementary analyses, as outlined in the Supplemental and Sensitivity Analyses.

Ethical approval

The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study. According to Danish law, ethical approval is not required for registry-based studies.

Software

All analyses were performed using STATA Release 14.1 (StataCorp, College Station, TX).

RESULTS

The study population comprised 71,533 case patients with BCC and 8629 case patients with SCC (Fig 1) who were matched with 1,430,883 and 172,462 population controls, respectively. Baseline characteristics were generally similar between case patients and controls, except that the BCC case patients were slightly better educated than the controls (Table I).

Overall, 2.7% of the BCC case patients and 2.1% of the controls were high users (≥50,000 mg) of HCTZ, yielding an adjusted OR of 1.29 (95% CI, 1.23-1.35) for BCC. The corresponding OR for SCC was 3.98 (95% CI, 3.68-4.31) based on high use of HCTZ in 10.0% of case patients and 2.8% of controls. Clear dose-response relationships were observed with

HCTZ use for both BCC and SCC, with the highest ORs observed in the upper exposure category (≥200,000 mg) (BCC: OR, 1.54; 95% CI, 1.38-1.71, test for trend $P < .001$; SCC: OR, 7.38; 95% CI, 6.32-8.60, test for trend $P < .001$ [Table II and Fig 2]). The proportion of skin cancers attributable to HCTZ use (ie, attributable proportion, see Methods) was 0.6% for BCC and 9.0% for SCC.

Little variation was seen in the association between HCTZ use and BCC or SCC risk in the subgroup analyses, except for notably stronger associations among younger individuals and females (Table II). In analyses stratified according to tumor localization, we observed stronger associations for cancers at sun-exposed skin sites, especially the skin of the lower limbs (Table III).

We found no associations for BCC or SCC risk with use of other diuretics and other hypertensives, including bendroflumethiazide, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, furosemide, indapamide, or nifedipine, neither overall or according to the cumulative use of the individual drugs (see Supplemental Tables I-VII in the Supplemental and Sensitivity Analyses).

In analyses excluding ever use of amiloride, HCTZ use exhibited dose to response relationships with the risk of BCC or SCC similar to those in the main analysis (Supplemental Table VIII in the Supplemental and Sensitivity Analyses), though small numbers precluded analyses of cumulative HCTZ use in excess of 100,000 mg.

DISCUSSION

In this large nationwide study including more than 70,000 patients with BCC and 8000 patients with SCC, we found a substantially increased risk of NMSC, particularly SCC, associated with HCTZ use. We observed clear dose-response patterns for both BCC and SCC, with a more than a 7-fold increased risk of SCC for a cumulative use of 200,000 mg or more of HCTZ. In addition, for both BCC and SCC, the associations with HCTZ use became stronger with increasing lag time before diagnoses. Assuming causality, the present results suggest that 1 of 11 SCC cases diagnosed during the study period can be attributed to HCTZ use. The increased risk of BCC and SCC appeared to be specific for HCTZ use among a range of examined drugs with similar indications.

The main strengths of our study include the population-based design and large sample

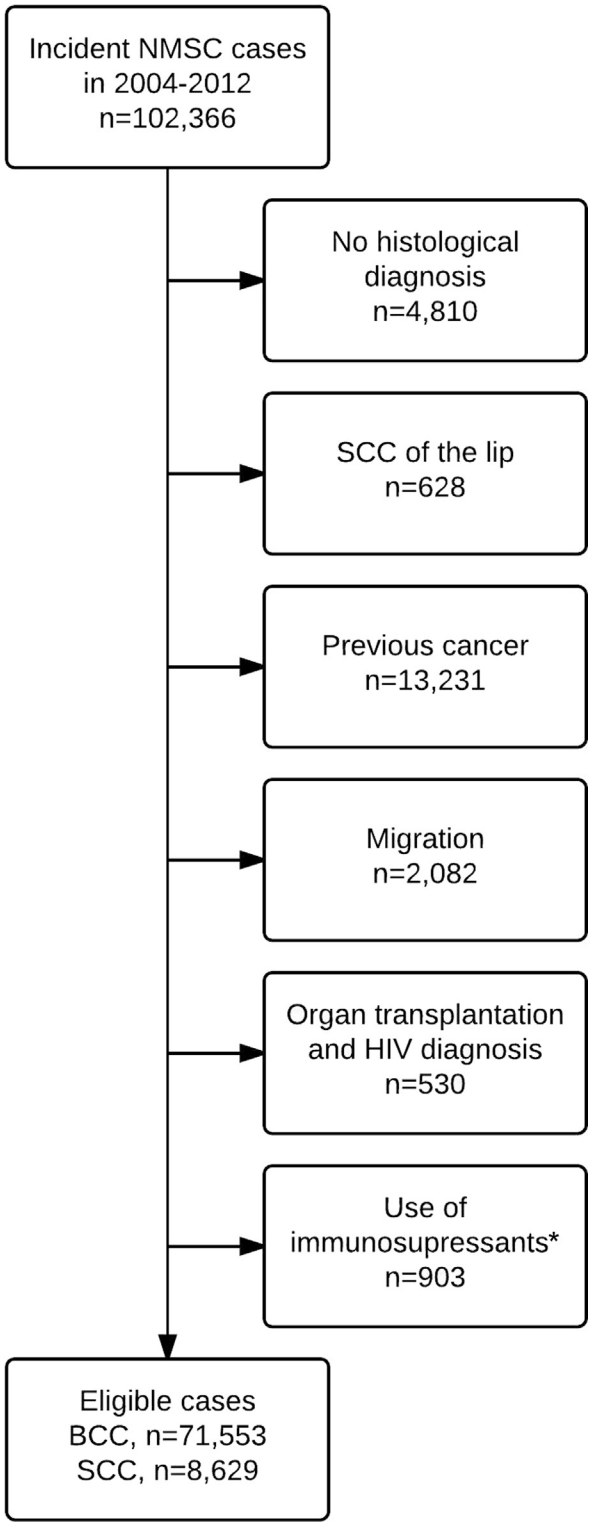

Fig 1. Flowchart of case selection. *Azathioprine, cyclosporine, and mycophenolate mofetil. *BCC*, Basal cell carcinoma; *NMSC*, nonmelanoma skin cancer; *SCC*, squamous cell carcinoma.

Table I. Characteristics of BCC and SCC cases and matched controls

Characteristic	BCC		SCC	
	Case patients (n = 71,553)	Controls (n = 1,430,883)	Case patients (n = 8629)	Controls (n = 172,462)
Age, median (IQR)	66 (57-76)	66 (57-76)	77 (68-85)	77 (68-85)
Male sex	33,817 (47.3%)	676,286 (47.3%)	4803 (55.7%)	96,020 (55.7%)
Use of HCTZ				
Never use	63,653 (89.0%)	1,281,894 (89.6%)	6817 (79.0%)	149,944 (86.9%)
Ever use	7900 (11.0%)	148,989 (10.4%)	1812 (21.0%)	22,518 (13.1%)
High use	1897 (2.7%)	30,075 (2.1%)	862 (10.0%)	4802 (2.8%)
Use of photosensitizing drugs				
Topical retinoids	197 (0.3%)	2279 (0.2%)	25 (0.3%)	168 (0.1%)
Oral retinoids	465 (0.6%)	5671 (0.4%)	46 (0.5%)	379 (0.2%)
Tetracycline	1563 (2.2%)	23,299 (1.6%)	170 (2.0%)	2310 (1.3%)
Macrolides	16,515 (23.1%)	295,632 (20.7%)	1860 (21.6%)	32,524 (18.9%)
Aminoquinolines	4405 (6.2%)	70,195 (4.9%)	605 (7.0%)	9324 (5.4%)
Amiodarone	370 (0.5%)	6106 (0.4%)	64 (0.7%)	1136 (0.7%)
Methoxypsoralene	50 (0.1%)	859 (0.1%)	13 (0.2%)	93 (0.1%)
Other drug use				
Aspirin	14,146 (19.8%)	284,771 (19.9%)	2955 (34.2%)	54,337 (31.5%)
Nonaspirin NSAID	37,353 (52.2%)	726,091 (50.7%)	4727 (54.8%)	89,452 (51.9%)
Statins	11,451 (16.0%)	226,657 (15.8%)	1779 (20.6%)	32,413 (18.8%)
Glucocorticoids	9057 (12.7%)	168,808 (11.8%)	1452 (16.8%)	24,456 (14.2%)
Diagnoses				
Alcohol-associated conditions	1881 (2.6%)	49,294 (3.4%)	221 (2.6%)	4491 (2.6%)
Diabetes	3884 (5.4%)	97,388 (6.8%)	783 (9.1%)	14,567 (8.4%)
COPD	3093 (4.3%)	66,770 (4.7%)	642 (7.4%)	10,947 (6.3%)
Chronic renal insufficiency	581 (0.8%)	12,031 (0.8%)	164 (1.9%)	2,114 (1.2%)
CCI score				
0	52,827 (73.8%)	1,045,348 (73.1%)	5132 (59.5%)	109,776 (63.7%)
1	11,454 (16.0%)	235,072 (16.4%)	1913 (22.2%)	36,079 (20.9%)
2	4132 (5.8%)	83,546 (5.8%)	827 (9.6%)	14,534 (8.4%)
≥3	3140 (4.4%)	66,917 (4.7%)	757 (8.8%)	12,073 (7.0%)
Education				
Short, 7-10 y	21,039 (29.4%)	523,901 (36.6%)	3252 (37.7%)	68,072 (39.5%)
Medium, 11-12 y	27,583 (38.5%)	509,694 (35.6%)	2619 (30.4%)	49,864 (28.9%)
Long, ≥13 y	18,265 (25.5%)	282,520 (19.7%)	1322 (15.3%)	24,771 (14.4%)
Unknown	4666 (6.5%)	114,768 (8.0%)	1436 (16.6%)	29,755 (17.3%)

Data are presented as n (%) unless otherwise noted.
BCC, Basal cell carcinoma; *CCI*, Charlson comorbidity index; *COPD*, chronic obstructive pulmonary disease; *HCTZ*, hydrochlorothiazide; *IQR*, interquartile range; *NSAID*, nonsteroidal anti-inflammatory drug; *SCC*, squamous cell carcinoma.

size based on high-quality nationwide registries including prescription data, medical conditions, and skin or other cancer diagnoses. Use of the Prescription Registry yielded complete and detailed long-term information on use of HCTZ or other drugs during an exposure period of up to 18 years.[15] Cancer diagnoses obtained from the Cancer Registry were restricted to histologically verified cases, further enhancing validity.[14]

This study also had some limitations. Most importantly, we did not have information on 2 major risk factors for BCC and SCC, namely, UV exposure and skin phenotype. However, we find it unlikely that sun habits would be markedly different between users and nonusers of HCTZ. We had no information on ethnicity or skin type; however, the majority of Danes are of white origin. Still, information on UV exposure and skin phenotype would have been useful in evaluating photosensitivity as the explanatory mechanism for an increased skin cancer risk with HCTZ use.

Severe skin photosensitivity reactions to HCTZ use have been reported.[23,24] In a recent survey of US dermatologists, patients with multiple SCC tumors reported a frequent history of HCTZ use.[25] However, only a few observational studies have investigated the association between HCTZ use and NMSC risk.[10-13] A Dutch study reported no association between

Table II. Association between exposure to hydrochlorothiazide and risk of NMSC according to cumulative hydrochlorothiazide use

Subgroup	Case patients	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	63,653	1,281,894	1.0 (ref)	1.0 (ref)
Ever use	7900	148,989	1.07 (1.04-1.10)	1.08 (1.05-1.10)
High use (≥50,000 mg)	1897	30,075	1.28 (1.22-1.34)	1.29 (1.23-1.35)
Cumulative amount				
1-9999 mg	2907	57,782	1.02 (0.98-1.06)	1.02 (0.98-1.06)
10,000-24,999 mg	1815	36,003	1.02 (0.97-1.07)	1.03 (0.98-1.08)
25,000-49,999 mg	1281	25,129	1.03 (0.97-1.09)	1.03 (0.97-1.09)
50,000-74,999 mg	511	9148	1.13 (1.03-1.24)	1.14 (1.04-1.25)
75,000-99,999 mg	271	4700	1.17 (1.03-1.32)	1.18 (1.04-1.33)
100,000-149,999 mg	395	6134	1.29 (1.17-1.43)	1.30 (1.17-1.44)
150,000-199,999 mg	329	4863	1.38 (1.23-1.54)	1.39 (1.24-1.56)
≥200,000 mg	391	5230	1.50 (1.35-1.67)	1.54 (1.38-1.71)
Squamous cell carcinoma				
Nonuse	6817	149,944	1.0 (ref)	1.0 (ref)
Ever use	1812	22,518	1.80 (1.70-1.90)	1.75 (1.66-1.85)
High use	862	4802	4.05 (3.75-4.39)	3.98 (3.68-4.31)
Cumulative amount				
1-9999 mg	392	8369	1.04 (0.93-1.15)	1.01 (0.91-1.12)
10,000-24,999 mg	283	5476	1.14 (1.01-1.29)	1.12 (0.99-1.27)
25,000-49,999 mg	275	3871	1.57 (1.38-1.78)	1.54 (1.36-1.75)
50,000-74,999 mg	133	1432	2.08 (1.74-2.50)	2.05 (1.70-2.46)
75,000-99,999 mg	95	746	2.89 (2.32-3.60)	2.84 (2.28-3.54)
100,000-149,999 mg	180	1104	3.65 (3.10-4.30)	3.56 (3.02-4.20)
150,000-199,999 mg	206	768	5.87 (5.00-6.89)	5.82 (4.96-6.84)
≥200,000 mg	248	752	7.53 (6.46-8.77)	7.38 (6.32-8.60)

CI, Confidence interval; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0, low; 2, medium; or ≥3, high); and (5) highest achieved education (short, medium, long, or unknown).

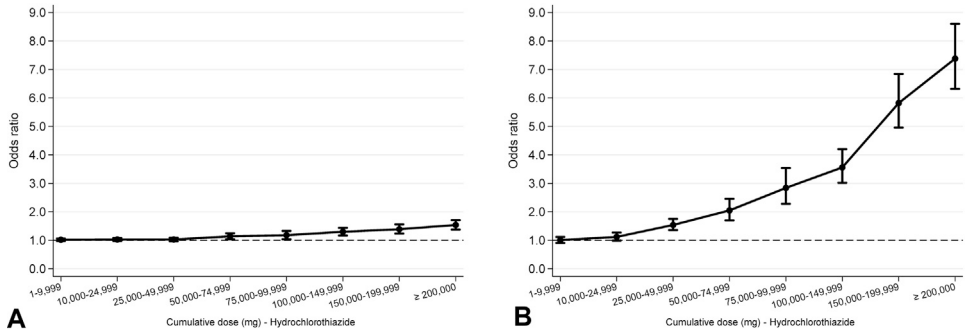

Fig 2. Dose-response pattern between cumulative hydrochlorothiazide dose and risk of basal cell carcinoma (**A**) and squamous cell carcinoma (**B**). Error bars represent 95% confidence intervals.

the use of thiazides (including HCTZ) and NMSC risk,[11] whereas a US study found that the use of diuretics overall was significantly associated with an increased risk of BCC.[26] The apparent discrepancy in the results of some previous studies and our findings are likely attributable to differences in exposure definition (HCTZ vs all thiazides) and outcomes (SCC vs BCC or NMSC only). A recent study from the United States found a relation between thiazide use and risk of SCC, but it did not present results for

Table III. Associations between high use of hydrochlorothiazide (≥50,000 mg) and risk of NMSC according to patient subgroups

Subgroup	Case patients exposed/unexposed	Controls exposed/unexposed	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
<50 y	20/9584	215/191,556	1.84 (1.16-2.91)	1.91 (1.20-3.03)
50-60 y	156/13,130	2431/263,283	1.29 (1.10-1.52)	1.38 (1.17-1.62)
60-75 y	854/26,068	13,403/522,436	1.27 (1.18-1.36)	1.29 (1.20-1.38)
≥75 y	867/14,871	14,026/304,619	1.27 (1.18-1.37)	1.26 (1.17-1.35)
Male	580/30,407	9308/612,587	1.26 (1.15-1.37)	1.26 (1.15-1.37)
Female	1317/33,246	20,767/669,307	1.28 (1.21-1.36)	1.31 (1.23-1.38)
Skin of head and neck	783/24,830	12,996/501,337	1.23 (1.14-1.32)	1.22 (1.13-1.31)
Skin of trunk	274/13,237	4815/264,068	1.12 (0.99-1.27)	1.19 (1.05-1.35)
Skin of upper limb	96/3003	1408/60,577	1.38 (1.11-1.70)	1.41 (1.14-1.75)
Skin of lower limb	114/2496	1513/50,153	1.51 (1.24-1.84)	1.55 (1.27-1.89)
Unspecified part of skin	630/20,087	9343/405,759	1.37 (1.26-1.49)	1.39 (1.27-1.51)
No use of photosensitizing drugs	1259/46,042	20,574/971,208	1.31 (1.23-1.39)	1.34 (1.26-1.43)
CCI score of 0	1103/48,163	17,284/957,511	1.29 (1.21-1.37)	1.28 (1.20-1.37)
No diabetes	1590/60,854	24,502/1,208,817	1.30 (1.23-1.37)	1.28 (1.21-1.35)
No psoriasis or atopic dermatitis	1841/61,975	29,299/1,253,574	1.27 (1.21-1.34)	1.29 (1.23-1.36)
No actinic keratosis	1881/63,512	29,998/1,281,028	1.27 (1.21-1.33)	1.29 (1.22-1.35)
Squamous cell carcinoma				
<50 y	7/258	(n < 5)	61.97 (12.81-299.74)	42.85 (8.31-220.84)
50-60 y	44/581	123/12,595	7.86 (5.48-11.28)	7.61 (5.24-11.04)
60-75 y	282/2429	1327/53,331	4.76 (4.15-5.47)	4.72 (4.10-5.44)
≥75 y	529/3549	3349/78,713	3.55 (3.21-3.92)	3.48 (3.15-3.85)
Male	281/3958	1844/84,936	3.32 (2.91-3.79)	3.26 (2.85-3.72)
Female	581/2859	2958/65,008	4.58 (4.15-5.05)	4.46 (4.04-4.94)
Skin of head and neck	292/2964	2188/64,025	2.92 (2.56-3.33)	2.83 (2.48-3.23)
Skin of trunk	46/632	345/13,429	2.93 (2.12-4.06)	2.95 (2.11-4.12)
Skin of upper limb	112/796	541/17,426	4.70 (3.76-5.87)	4.90 (3.90-6.16)
Skin of lower limb	101/482	422/11,115	5.80 (4.54-7.41)	5.88 (4.57-7.56)
Unspecified part of skin	311/1943	1306/43,949	5.57 (4.86-6.38)	5.42 (4.72-6.23)
No use of photosensitizing drugs	567/5053	3380/115,858	3.99 (3.62-4.41)	3.96 (3.59-4.38)
CCI score of 0	464/4223	2618/97,620	4.29 (3.83-4.81)	4.19 (3.74-4.70)
No diabetes	727/6338	3948/138,972	4.13 (3.79-4.50)	4.02 (3.68-4.38)
No psoriasis or atopic dermatitis	823/6608	4679/146,952	4.00 (3.69-4.33)	3.94 (3.63-4.27)
No actinic keratosis	839/6762	4791/149,785	3.98 (3.68-4.31)	3.92 (3.62-4.25)

CCI, Charlson comorbidity index; *CI*, confidence interval; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio.
*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.
†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0, low; 2, medium; or ≥3, high); and (5) highest achieved education (short, medium, long, or unknown).

individual thiazides.[27] Only 2 previous studies reported results specifically for HCTZ. A Danish study observed an increased risk of SCC, but not BCC, with the use of HCTZ alone and in combination with amiloride. However, this study had a limited exposure period and relatively small sample size based on only 1 of 5 Danish regions, thus precluding detailed analyses of cumulative HCTZ use.[12] A more recent study from the same region also noted an increased risk of SCC associated with using the combination of HCTZ and amiloride. However, the association was not further explored and no dose-response analyses were presented.[10]

SCC was more strongly associated with HCTZ use than was BCC, which is in line with the evidence that cumulative UV exposure plays a larger role in the etiology of SCC than of BCC.[1] Furthermore, the observed associations varied according to body site and were stronger for the limbs than for the trunk, which is compatible with the notion that the increased NMSC risk associated with HCTZ use is mediated through a

photosensitizing effect. The difference in associations according to sex may be related to differences in skin thickness (ie, women have a thinner layer of both epidermis and dermis than men)[28] and sun habits (ie, women are more frequent tanners than men),[29] which may confer a difference in susceptibility to the effects of photosensitizing exposure.

The associations with HCTZ use also varied according to age, with the highest ORs for both BCC (1.91) and SCC (42.85) observed among persons younger than 50 years. The stronger association among the youngest subjects strengthens the argument for a photosensitizing effect. The decrease in ORs (ie, a measure of relative risk) with increasing age may also reflect that NMSC risk increases with age for other reasons (eg, accumulation of DNA breaks and immunosenescence).

Lastly (and in line with our previous study), we found no association between the use of other antihypertensive drugs and NMSC risk.[6] In addition to the strength of the observed associations, the specificity of HCTZ use with increased risk of BCC and SCC supports the potential causal association between HCTZ use and NMSC risk.

In conclusion, given the considerable use of HCTZ worldwide and the morbidity associated with NMSC, a causal association between HCTZ use and NMSC risk would have significant public health implications. The use of HCTZ should be carefully considered, as several other antihypertensive agents with similar indications and efficiency are available, but without known associations with skin cancer.

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SUPPLEMENTAL AND SENSITIVITY ANALYSES

First, we repeated the main analyses for other diuretic drugs with suggested photosensitizing properties, including bendroflumethiazide and furosemide.[10,12,13] Next, we performed analyses for other antihypertensives, including angiotensin-converting enzyme inhibitors, angiotesin II receptor blockers, and calcium channel blockers. In the analyses of other diuretics and nondiuretic antihypertensives, associations were adjusted for hydrochlorothiazide (HCTZ) use. In addition, we excluded ever-users of amiloride from the main analyses to obtain risk estimates for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with HCTZ use exclusive of amiloride (primarily preparations of HCTZ and angiotensin-converting enzyme inhibitors or angiotesin II receptor blockers). On the basis of the results from the categoric dose-response analyses, the attributable proportion of HCTZ use for BCC and SCC (assuming causality) was estimated by adding the single steps in the dose-response analysis together (estimated as attributable proportion = (odds ratio − 1)/odds ratio). Finally, we examined associations between HCTZ use and BCC or SCC risk according to tumor localization, categorized as skin of the head and neck, skin of the trunk, skin of the upper limb, skin of the lower limb, and unspecified part of the skin.

Supplemental Table I. Association between exposure to bendroflumethiazide and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	53,800	1,081,784	1.0 (ref)	1.0 (ref)
Ever use	17,753	349,099	1.03 (1.01-1.04)	1.03 (1.01-1.05)
High use (≥50,000 mg)	4207	81,884	1.03 (1.00-1.07)	1.06 (1.02-1.09)
Cumulative amount				
1-999 mg	7130	138,711	1.04 (1.01-1.06)	1.04 (1.01-1.07)
1000-2499 mg	3384	67,970	1.00 (0.97-1.04)	1.02 (0.98-1.06)
2500-4999 mg	3032	60,534	1.01 (0.97-1.05)	1.02 (0.98-1.06)
5000-7499 mg	1770	33,840	1.06 (1.00-1.11)	1.08 (1.02-1.13)
7500-9999 mg	1078	20,815	1.04 (0.98-1.11)	1.07 (1.00-1.14)
≥10,000 mg	1359	27,229	1.00 (0.95-1.06)	1.03 (0.97-1.09)
Squamous cell carcinoma				
Nonuse	5717	115,881	1.0 (ref)	1.0 (ref)
Ever use	2912	56,581	1.05 (1.00-1.10)	1.02 (0.97-1.08)
High use	691	14,669	0.93 (0.86-1.02)	0.98 (0.90-1.07)
Cumulative amount				
1-999 mg	1165	20,507	1.14 (1.07-1.22)	1.09 (1.01-1.16)
1000-2499 mg	560	11,079	1.01 (0.92-1.11)	0.99 (0.90-1.09)
2500-4999 mg	496	10,326	0.96 (0.87-1.06)	0.97 (0.88-1.07)
5000-7499 mg	313	5962	1.04 (0.92-1.17)	1.06 (0.94-1.20)
7500-9999 mg	166	3786	0.86 (0.73-1.01)	0.92 (0.78-1.09)
≥10,000 mg	212	4921	0.84 (0.73-0.97)	0.92 (0.79-1.06)

CI, Confidence interval; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0, low; 2, medium; or ≥3, high); and (5) highest achieved education (short, medium, long, or unknown).

Supplemental Table II. Association between exposure to furosemide and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	63,951	1,270,426	1.0 (ref)	1.0 (ref)
Ever use	7602	160,457	0.94 (0.91-0.96)	0.94 (0.92-0.97)
High use (≥2000 DDD)	1984	43,784	0.90 (0.86-0.94)	0.93 (0.89-0.98)
Cumulative dose (DDD)				
1-399	3527	71,788	0.97 (0.94-1.01)	0.97 (0.93-1.00)
400-999	1107	24,040	0.92 (0.86-0.98)	0.93 (0.88-0.99)
1000-1999	984	20,844	0.94 (0.88-1.00)	0.96 (0.90-1.03)
2000-2999	572	12,792	0.89 (0.81-0.96)	0.91 (0.84-1.00)
3000-3999	430	9119	0.93 (0.85-1.03)	0.97 (0.87-1.07)
≥4000	982	21,873	0.90 (0.84-0.96)	0.94 (0.88-1.01)
Squamous cell carcinoma				
Nonuse	6799	141,645	1.0 (ref)	1.0 (ref)
Ever use	1830	30,817	1.26 (1.19-1.33)	1.11 (1.05-1.18)
High use (≥2000 DDD)	611	9609	1.34 (1.23-1.46)	1.18 (1.07-1.30)
Cumulative amount				
1-399	715	12,038	1.25 (1.15-1.35)	1.11 (1.02-1.21)
400-999	250	4695	1.11 (0.97-1.26)	0.98 (0.86-1.13)
1000-1999	254	4475	1.20 (1.05-1.37)	1.07 (0.93-1.23)
2000-2999	169	2858	1.25 (1.07-1.47)	1.10 (0.93-1.30)
3000-3999	127	1862	1.42 (1.18-1.71)	1.26 (1.04-1.52)
≥4000	315	4889	1.36 (1.20-1.53)	1.23 (1.08-1.40)

CI, Confidence interval; *DDD*, defined daily dose; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0: low; 2: medium; or ≥3: high); and (5) highest achieved education (short, medium, long, or unknown).

Supplemental Table III. Association between exposure to calcium channel blockers and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	60,645	1,222,633	1.0 (ref)	1.0 (ref)
Ever use	10,908	208,250	1.06 (1.04-1.08)	1.07 (1.04-1.09)
High use (≥2000 DDD)	3630	66,445	1.11 (1.07-1.15)	1.13 (1.09-1.17)
Cumulative dose (DDD)				
1-399	3321	64,908	1.04 (1.00-1.08)	1.04 (1.00-1.08)
400-999	2078	39,428	1.06 (1.02-1.11)	1.07 (1.02-1.12)
1000-1999	1879	37,468	1.02 (0.97-1.07)	1.03 (0.98-1.08)
2000-2999	1223	23,378	1.07 (1.01-1.13)	1.08 (1.02-1.15)
3000-3999	858	15,491	1.14 (1.06-1.22)	1.16 (1.08-1.24)
≥4000	1549	27,576	1.14 (1.08-1.20)	1.16 (1.10-1.22)
Squamous cell carcinoma				
Nonuse	6780	138,113	1.0 (ref)	1.0 (ref)
Ever use	1849	34,349	1.10 (1.04-1.16)	0.98 (0.93-1.04)
High use (≥2000 DDD)	627	11,514	1.12 (1.03-1.22)	0.98 (0.90-1.08)
Cumulative dose (DDD)				
1-399	548	10,382	1.08 (0.99-1.18)	0.97 (0.88-1.07)
400-999	356	6311	1.15 (1.03-1.29)	1.05 (0.94-1.18)
1000-1999	318	6142	1.05 (0.93-1.18)	0.93 (0.83-1.05)
2000-2999	218	4006	1.11 (0.96-1.27)	0.97 (0.84-1.12)
3000-3999	143	2770	1.05 (0.88-1.25)	0.93 (0.78-1.11)
≥4000	266	4738	1.16 (1.02-1.32)	1.03 (0.90-1.17)

CI, Confidence interval; *DDD*, defined daily dose; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0, low; 2, medium; or ≥3, high); and (5) highest achieved education (short, medium, long, or unknown).

Supplemental Table IV. Association between exposure to ACE inhibitors and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	58,669	1,167,222	1.0 (ref)	1.0 (ref)
Ever use	12,884	263,661	0.97 (0.95-0.99)	0.98 (0.96-1.00)
High use (≥2000 DDD)	3889	79,623	0.97 (0.94-1.01)	0.99 (0.96-1.03)
Cumulative dose (DDD)				
1-399	4632	92,798	0.99 (0.96-1.03)	1.00 (0.96-1.03)
400-999	2317	47,961	0.96 (0.92-1.01)	0.97 (0.93-1.02)
1000-1999	2046	43,278	0.94 (0.90-0.99)	0.96 (0.91-1.01)
2000-2999	1235	25,624	0.95 (0.90-1.01)	0.97 (0.92-1.03)
3000-3999	796	16,561	0.96 (0.89-1.03)	0.97 (0.90-1.04)
≥4000	1858	37,439	1.00 (0.95-1.05)	1.02 (0.97-1.07)
Squamous cell carcinoma				
Nonuse	6331	130,503	1.0 (ref)	1.0 (ref)
Ever use	2298	41,959	1.14 (1.08-1.20)	1.00 (0.95-1.06)
High use (≥2000 DDD)	735	13,034	1.18 (1.09-1.28)	1.00 (0.92-1.09)
Cumulative dose (DDD)				
1-399	742	14,421	1.05 (0.97-1.14)	0.96 (0.88-1.04)
400-999	416	7545	1.15 (1.04-1.28)	1.05 (0.95-1.18)
1000-1999	405	6959	1.20 (1.08-1.34)	1.09 (0.98-1.22)
2000-2999	198	4203	0.98 (0.85-1.13)	0.87 (0.74-1.01)
3000-3999	164	2757	1.25 (1.06-1.47)	1.07 (0.91-1.27)
≥4000	373	6074	1.28 (1.15-1.43)	1.08 (0.96-1.22)

ACE, Angiotensin-converting enzyme; *CI*, confidence interval; *DDD*, defined daily dose; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index (CCI) score (0, low; 2, medium; or ≥3, high); and (5) highest achieved education (short, medium, long, or unknown).

Supplemental Table V. Association between exposure to angiotensin II receptor antagonists and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	63,470	1,278,247	1.0 (ref)	1.0 (ref)
Ever use	8083	152,636	1.07 (1.04-1.10)	1.06 (1.03-1.09)
High use (≥2000 DDD)	2659	48,517	1.11 (1.07-1.16)	1.08 (1.03-1.13)
Cumulative dose (DDD)				
1-399	2086	39,981	1.06 (1.01-1.11)	1.05 (1.00-1.10)
400-999	1508	29,309	1.04 (0.99-1.10)	1.04 (0.98-1.10)
1000-1999	1830	34,829	1.06 (1.01-1.12)	1.05 (1.00-1.11)
2000-2999	1250	22,591	1.12 (1.05-1.18)	1.09 (1.03-1.17)
3000-3999	680	13,081	1.06 (0.98-1.15)	1.03 (0.95-1.12)
≥4000	729	12,845	1.15 (1.07-1.24)	1.10 (1.02-1.19)
Squamous cell carcinoma				
Nonuse	7353	149,367	1.0 (ref)	1.0 (ref)
Ever use	1276	23,095	1.13 (1.06-1.20)	0.93 (0.87-1.00)
High use (≥2000 DDD)	457	7549	1.23 (1.12-1.36)	0.88 (0.79-0.99)
Cumulative dose (DDD)				
1-399	327	5972	1.10 (0.98-1.24)	0.99 (0.88-1.12)
400-999	231	4336	1.08 (0.94-1.23)	0.95 (0.82-1.09)
1000-1999	261	5238	1.01 (0.89-1.15)	0.84 (0.73-0.97)
2000-2999	192	3542	1.10 (0.94-1.27)	0.82 (0.70-0.97)
3000-3999	136	1982	1.41 (1.18-1.68)	0.97 (0.81-1.18)
≥4000	129	2025	1.30 (1.08-1.56)	0.86 (0.71-1.04)

CI, Confidence interval; *DDD*, defined daily dose; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0, low; 2, medium; or ≥3, high); and (5) highest achieved education (short, medium, long, or unknown).

Supplemental Table VI. Association between exposure to indapamide and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	70,838	1,416,467	1.0 (ref)	1.0 (ref)
Ever use	715	14,416	0.99 (0.92-1.07)	0.99 (0.92-1.07)
High use (≥2000 DDD)	44	911	0.97 (0.71-1.31)	0.97 (0.72-1.32)
Cumulative dose (DDD)				
1-399	383	8150	0.94 (0.85-1.04)	0.94 (0.85-1.04)
400-999	191	3584	1.07 (0.92-1.24)	1.07 (0.92-1.24)
1000-1999	97	1771	1.10 (0.90-1.35)	1.11 (0.90-1.36)
2000-2999	23	516	0.88 (0.58-1.34)	0.88 (0.58-1.34)
3000-3999	15	240	1.25 (0.74-2.11)	1.28 (0.76-2.15)
≥4000	6	155	0.79 (0.35-1.79)	0.81 (0.36-1.83)
Squamous cell carcinoma				
Nonuse	8511	170,073	1.0 (ref)	1.0 (ref)
Ever use	118	2389	0.99 (0.82-1.19)	0.95 (0.79-1.15)
High use (≥2000 DDD)	7	178	0.78 (0.37-1.67)	0.84 (0.39-1.79)
Cumulative dose (DDD)				
1-399	67	1324	1.01 (0.79-1.29)	0.97 (0.75-1.24)
400-999	28	589	0.94 (0.65-1.38)	0.89 (0.61-1.31)
1000-1999	16	298	1.08 (0.65-1.78)	1.06 (0.64-1.77)
2000-2999	(n<5)	109	—	—
3000-3999	(n<5)	49	—	—
≥4000	(n<5)	20	—	—

CI, Confidence interval; *DDD*, defined daily dose; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0, low; 2, medium; or ≥3, high); and (5) highest achieved education (short, medium, long, or unknown).

Supplemental Table VII. Association between exposure to nifedipine and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	70,563	1,412,975	1.0 (ref)	1.0 (ref)
Ever use	990	17,908	1.11 (1.04-1.18)	1.10 (1.03-1.17)
High use (≥2000 DDD)	228	4206	1.08 (0.95-1.24)	1.08 (0.95-1.24)
Cumulative dose (DDD)				
1-399	514	9216	1.12 (1.02-1.22)	1.10 (1.01-1.21)
400-999	117	2339	1.00 (0.83-1.20)	0.99 (0.82-1.20)
1000-1999	131	2147	1.23 (1.03-1.46)	1.23 (1.03-1.46)
2000-2999	61	1342	0.90 (0.70-1.17)	0.89 (0.69-1.15)
3000-3999	53	923	1.15 (0.88-1.52)	1.16 (0.88-1.53)
≥4000	114	1941	1.17 (0.97-1.42)	1.18 (0.98-1.43)
Squamous cell carcinoma				
Nonuse	8466	169,467	1.0 (ref)	1.0 (ref)
Ever use	163	2995	1.09 (0.93-1.28)	0.97 (0.82-1.14)
High use (≥2000 DDD)	48	754	1.28 (0.95-1.71)	1.15 (0.85-1.54)
Cumulative dose (DDD)				
1-399	71	1416	1.00 (0.79-1.27)	0.89 (0.70-1.14)
400-999	26	449	1.16 (0.78-1.72)	0.99 (0.66-1.48)
1000-1999	18	376	0.96 (0.60-1.54)	0.86 (0.54-1.39)
2000-2999	18	215	1.70 (1.05-2.75)	1.56 (0.96-2.54)
3000-3999	9	177	1.01 (0.52-1.98)	0.99 (0.50-1.94)
≥4000	21	362	1.16 (0.75-1.80)	0.99 (0.63-1.54)

CI, Confidence interval; *DDD*, defined daily dose; *NMSC*, nonmelanoma skin cancer; OR, odds ratio; ref, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0: low; 2: medium; or ≥3: high); and (5) highest achieved education (short, medium, long, or unknown).

Supplemental Table VIII. Association between exposure to hydrochlorothiazide and risk of NMSC according to the cumulative hydrochlorothiazide use, restricted to never-users of amiloride

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Basal cell carcinoma				
Nonuse	63,520	1,278,990	1.0 (ref)	1.0 (ref)
Ever use	5033	99,508	1.02 (0.99-1.05)	1.03 (1.00-1.06)
High use (≥50,000 mg)	382	6457	1.19 (1.07-1.32)	1.21 (1.09-1.34)
Cumulative amount				
1-9999 mg	2216	44,331	1.01 (0.97-1.06)	1.02 (0.97-1.06)
10,000-24,999 mg	1478	29,727	1.01 (0.96-1.07)	1.02 (0.96-1.07)
25,000-49,999 mg	957	18,993	1.01 (0.95-1.08)	1.02 (0.95-1.09)
50,000-74,999 mg	281	4792	1.18 (1.05-1.33)	1.20 (1.06-1.35)
75,000-99,999 mg	74	1173	1.27 (1.00-1.60)	1.29 (1.02-1.64)
100,000-149,999 mg	25	429	1.16 (0.77-1.73)	1.19 (0.79-1.78)
150,000-199,999 mg	(n<5)	48	—	—
≥200,000 mg	(n<5)	15	—	—
Squamous cell carcinoma				
Nonuse	6786	149,391	1.0 (ref)	1.0 (ref)
Ever use	754	14,629	1.14 (1.06-1.24)	1.13 (1.04-1.22)
High use	81	967	1.89 (1.50-2.39)	1.89 (1.50-2.39)
Cumulative amount				
1-9999 mg	285	6334	1.00 (0.88-1.13)	0.98 (0.87-1.11)
10,000-24,999 mg	213	4459	1.06 (0.92-1.21)	1.05 (0.91-1.21)
25,000-49,999 mg	175	2869	1.36 (1.16-1.59)	1.35 (1.16-1.58)
50,000-74,999 mg	56	729	1.74 (1.32-2.29)	1.73 (1.31-2.28)
75,000-99,999 mg	12	181	1.58 (0.87-2.86)	1.60 (0.88-2.90)
100,000-149,999 mg	9	48	3.75 (1.81-7.77)	3.74 (1.80-7.76)
150,000-199,999 mg	(n<5)	9	—	—
≥200,000 mg	(n<5)	(n<5)	—	—

CI, Confidence interval; *NMSC*, nonmelanoma skin cancer; *OR*, odds ratio; *ref*, reference.

*Adjusted for age, sex, and calendar time by risk-set matching and the conditional analysis.

†Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; (2) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or statins; (3) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; (4) Charlson comorbidity index score (0: low; 2: medium; or ≥3: high); and (5) highest achieved education (short, medium, long, or unknown).