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

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Conflicts of interest
Anton Pottegård has participated in research projects unrelated to the present study using grants provided by LEO Pharma (manufacturer of bendroflumethiazide) to the institution where he was employed. David Gaist received honoraria from AstraZeneca (Sweden) for participating as a coinvestigator in a research project outside this work. The remaining authors declare no relevant conflicts of interest.

Ethical approval
In Denmark, ethical approval is not required for purely registry based studies.

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Abstract

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 NMSC during 2004-2012. Controls were matched 1:20 by age and sex. Cumulative hydrochlorothiazide use (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 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 was available.

Conclusions

Hydrochlorothiazide use is associated with a substantially increased risk of NMSC, especially SCC.

Key words

Hydrochlorothiazide, antihypertensives, skin cancer, pharmacology, epidemiology

Introduction

Non-melanoma 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 (e.g., cyclosporine and azathioprine) induces NMSC, and other drugs have been suggested to either increase (e.g., topical and systemic calcineurin inhibitors) or decrease (e.g., aspirin and other non-steroidal anti-inflammatory drugs [NSAIDs]) the risk of NMSC.[2–5]

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 HCTZ. Our findings were in line with the results of previous studies from the United States (US)[7] and the recent classification of HCTZ as 'possibly carcinogenic to humans' (Group 2B) by the International Agency for Research on Cancer (IARC).[8] As HCTZ is among the most widely used drugs in the US 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 other antihypertensives, as HCTZ is mainly prescribed in combination with other diuretics (primarily amiloride) or non-diuretic antihypertensives.[10–13] Therefore, we were interested in examining the association between HCTZ use and NMSC risk more extensively, and to evaluate 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 diagnosed with SCC and BCC of the skin to 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 five 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 NMSC patients

NMSC patients were Danish residents with histological verification of their first diagnosis of SCC or BCC of the skin between January 1, 2004, and December 31, 2012. We excluded cases with SCC of the lip, as they were evaluated in our previous study.[6] We required cases to have no previous skin or other cancer diagnoses prior to the first diagnosis of BCC or SCC (index date) and to have resided in Denmark for at least 10 consecutive years prior to the index date. We also required cases 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 cases, the

calculated ORs provide unbiased estimates of the incidence rate ratios that would have emerged from a cohort study based on the source population.

Exposure definition

Based on prescription data from 1995 onwards, ever-use of HCTZ was defined as having filled at least one prescription of an HCTZ-containing drug prior to index date and never-use as no HCTZ-containing prescription. In Denmark, HCTZ is prescribed almost exclusively as combination preparations with potassium-sparing diuretic amiloride or non-diuretic antihypertensives, predominantly angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARBs). The content of HCTZ was identified in all combination or single drugs dispensed to individuals in the study population and based on this information the cumulative dose of HCTZ each individual had been exposed to up to index date was calculated. High use of HCTZ was defined as filled prescriptions equivalent to ≥50,000 mg of HCTZ, corresponding to ≥2,000 defined daily doses (DDDs) (i.e., ~6 years of cumulative use). Prescriptions filled within 2 years prior to 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 prior to the skin cancer diagnosis influenced the decision to prescribe HCTZ.[20]

Other variables

We defined potential confounders based on the following data: a) use of selected drugs with suggested photosensitizing properties, including oral retinoids, topical retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene;[10,13,21,22] b) use of drugs with suggested anti-neoplastic effects, including aspirin, NSAIDs, and statins;[3] c) composite measures of hospital diagnoses and disease-specific drugs defining medical histories of diabetes, chronic obstructive pulmonary disease (COPD), chronic renal insufficiency, or conditions associated with heavy alcohol consumption (see Appendix B); d) Charlson Comorbidity Index (CCI) scores (0: low; 1-2: medium; or ≥3: high) derived from the prevalence of 19 chronic conditions; and f) highest achieved education (basic, medium, higher, or unknown). Exposure to each potential confounder drug was defined as two 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 prior to 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 pre-defined 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 restricting to HCTZ ever users and estimating the incremental OR for each 10,000mg HCTZ, 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 never-use of HCTZ served as the reference group unless stated otherwise. We performed a number of preplanned supplementary analyses, as outlined in **Appendix A**.

184 **Ethical approval**

185 The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study.

186 According to Danish law, ethical approval is not required for registry-based studies.

187

188 **Other**

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

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194 **Results**

195 The study population comprised 71,533 BCC and 8,629 SCC cases (**Figure 1**) that were matched to
196 1,430,883 and 172,462 population controls, respectively. Baseline characteristics were generally similar
197 between cases and controls, except that BCC cases were slightly more educated than controls (**Table**
198 **1**).

199 Overall, 2.7% of BCC cases and 2.1% of controls were high users (≥50,000 mg) of
200 HCTZ, yielding an adjusted OR of 1.29 (95% CI 1.23-1.35) for BCC. The corresponding OR for SCC
201 was 3.98 (95% CI 3.68-4.31) based on high use of HCTZ in 10.0% of cases and 2.8% of controls. Clear
202 dose-response relationships were observed with HCTZ use for both BCC and SCC, with the highest
203 ORs observed in the upper exposure category (≥200,000 mg) (BCC: OR 1.54, 95% CI 1.38-1.71, test
204 for trend p<0.001; SCC: OR 7.38; 95% CI 6.32-8.60, test for trend p<0.001; **Table 2** and **Figure 2**).
205 The proportion of skin cancers attributable to HCTZ use (i.e., AP, see Methods) was 0.6% for BCC
206 and 9.0% for SCC.

207 Little variation was seen in the association between HCTZ use and BCC or SCC risk in
208 the subgroup analyses, except for notably stronger associations among younger individuals and females
209 (**Table 3**). In analyses stratified according to tumor localization, we observed stronger associations for
210 cancers at sun-exposed skin sites, especially the skin of the lower limbs (**Table 3**).

211 We found no associations for BCC or SCC risk with use of other diuretics and other
212 hypertensives, including bendroflumethiazide, CCBs, ACE inhibitors, ARBs, furosemide, indapamide,
213 or nifedipine, neither overall or according to the cumulative use of the individual drugs
214 (**Supplementary Results Ia-g**).

215 In analyses excluding ever-use of amiloride, HCTZ use exhibited dose to response
216 relationships with the risk of BCC or SCC similar to those in the main analysis (**Supplementary**
217 **results II**), though small numbers precluded an analysis of cumulative HCTZ use above 100,000 mg.

218

219

Discussion

In this large nationwide study including more than 70,000 BCC and 8,000 SCC patients, 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 7-fold increased risk of SCC for a cumulative use of ≥200,000 mg HCTZ. In addition, for both BCC and SCC, the associations with HCTZ use became stronger with increasing lag time prior to diagnoses. Assuming causality, the present results suggest that 1 of 10 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 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 HCTZ or other drug use 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 two major risk factors for BCC and SCC, UV exposure and skin phenotype. However, we find it unlikely that sun habits would be markedly different between users and non-users of HCTZ. We had no information on ethnicity or skin type, however, the majority of Danes are of Caucasian 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 the use of thiazides (including HCTZ) and NMSC risk,[11] whereas a US study found that the use of diuretics overall was significantly

246 associated with an increased risk of BCC.[26] The apparent discrepancy in the results of some previous
247 studies and our findings are likely attributable to differences in exposure definition (HCTZ versus 'all
248 thiazides') and outcomes (SCC versus BCC or NMSC only). A recent study from the US found a
249 relation between thiazide use and risk of SCC, but did not present results for individual thiazides.[27]
250 Only two previous studies reported results specifically for HCTZ. A Danish study observed an
251 increased risk of SCC, but not BCC, with the use of HCTZ alone and in combination with amiloride.
252 However, this study had a limited exposure period and relatively small sample size based on only one of
253 five Danish regions, precluding detailed analyses of cumulative HCTZ use.[12] A more recent study from
254 the same region also noted an increased risk of SCC associated with using the combination of HCTZ
255 and amiloride. However, the association was not further explored and no dose-response analyses were
256 presented.[10]

257 SCC was more strongly associated with HCTZ use than BCC, which is in line with the
258 evidence that cumulative UV exposure plays a larger role in the etiology of SCC than of BCC[1].
259 Furthermore, the observed associations varied according to body site and were stronger for the limbs
260 than for the trunk, which is compatible with the notion that the increased NMSC risk associated with
261 HCTZ use is mediated through a photosensitizing effect. The difference in associations according to
262 sex may be related to differences in skin thickness (i.e., women have a thinner layer of both epidermis
263 and dermis than men)[28] and sun habits (i.e., women are more frequent tanners than men)[29] may confer a
264 difference in susceptibility to the effects of photosensitizing exposure.

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

270 Lastly, and in line with our previous study, we found no association between the use of
271 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 this evidence 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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368 **Figures and tables**

369

370 **Figure 1:** Flowchart of case selection

371 [1]Azathioprine, cyclosporine, and mycophenolate mofetil.

372

373 **Figure 2:** Dose-response pattern between cumulative HCTZ dose and risk of (A) BCC and (B) SCC. .

374 Error bars represent 95% confidence intervals.

375 **A)**

376 **B)**

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380 **Table 1**

381 Characteristics of BCC and SCC cases and matched controls

382

	BCC		SCC	
	Cases (n=71,553)	**Controls** (n=1,430,883)	**Cases** (n=8,629)	**Controls** (n=172,462)
Age, median (IQR)	66 (57-76)	66 (57-76)	77 (68-85)	77 (68-85)
Male gender	33,817 (47.3%)	676,286 (47.3%)	4,803 (55.7%)	96,020 (55.7%)
Use of HCTZ				
Never-use	63,653 (89.0%)	1,281,894 (89.6%)	6,817 (79.0%)	149,944 (86.9%)
Ever-use	7,900 (11.0%)	148,989 (10.4%)	1,812 (21.0%)	22,518 (13.1%)
High-use	1,897 (2.7%)	30,075 (2.1%)	862 (10.0%)	4,802 (2.8%)
Use of photosens. drugs				
Topical retinoids	197 (0.3%)	2,279 (0.2%)	25 (0.3%)	168 (0.1%)
Oral retinoids	465 (0.6%)	5,671 (0.4%)	46 (0.5%)	379 (0.2%)
Tetracycline	1,563 (2.2%)	23,299 (1.6%)	170 (2.0%)	2,310 (1.3%)
Macrolides	16,515 (23.1%)	295,632 (20.7%)	1,860 (21.6%)	32,524 (18.9%)
Aminoquinolines	4,405 (6.2%)	70,195 (4.9%)	605 (7.0%)	9,324 (5.4%)
Amiodarone	370 (0.5%)	6,106 (0.4%)	64 (0.7%)	1,136 (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%)	2,955 (34.2%)	54,337 (31.5%)
Non-aspirin NSAID	37,353 (52.2%)	726,091 (50.7%)	4,727 (54.8%)	89,452 (51.9%)
Statins	11,451 (16.0%)	226,657 (15.8%)	1,779 (20.6%)	32,413 (18.8%)
Glucocorticoids	9,057 (12.7%)	168,808 (11.8%)	1,452 (16.8%)	24,456 (14.2%)
Diagnoses				
Alcohol-associated conditions	1,881 (2.6%)	49,294 (3.4%)	221 (2.6%)	4,491 (2.6%)
Diabetes	3,884 (5.4%)	97,388 (6.8%)	783 (9.1%)	14,567 (8.4%)
COPD	3,093 (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%)	5,132 (59.5%)	109,776 (63.7%)
1	11,454 (16.0%)	235,072 (16.4%)	1,913 (22.2%)	36,079 (20.9%)
2	4,132 (5.8%)	83,546 (5.8%)	827 (9.6%)	14,534 (8.4%)
≥3	3,140 (4.4%)	66,917 (4.7%)	757 (8.8%)	12,073 (7.0%)
Education				
Short, 7-10 years	21,039 (29.4%)	523,901 (36.6%)	3,252 (37.7%)	68,072 (39.5%)
Medium, 11-12 years	27,583 (38.5%)	509,694 (35.6%)	2,619 (30.4%)	49,864 (28.9%)
Long, ≥13 years	18,265 (25.5%)	282,520 (19.7%)	1,322 (15.3%)	24,771 (14.4%)
Unknown	4,666 (6.5%)	114,768 (8.0%)	1,436 (16.6%)	29,755 (17.3%)

Data are presented as n (%) unless otherwise noted.
HCTZ = Hydrochlorothiazide
IQR = Interquartile range
CCI = Charlson Comorbidity Index

Table 2

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

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	63,653	1,281,894	1.0 (ref.)	1.0 (ref.)
Ever use	7,900	148,989	1.07 (1.04-1.10)	1.08 (1.05-1.10)
High use (≥50,000 mg)	1,897	30,075	1.28 (1.22-1.34)	1.29 (1.23-1.35)
Cumulative amount				
1-9,999 mg	2,907	57,782	1.02 (0.98-1.06)	1.02 (0.98-1.06)
10,000-24,999 mg	1,815	36,003	1.02 (0.97-1.07)	1.03 (0.98-1.08)
25,000-49,999 mg	1,281	25,129	1.03 (0.97-1.09)	1.03 (0.97-1.09)
50,000-74,999 mg	511	9,148	1.13 (1.03-1.24)	1.14 (1.04-1.25)
75,000-99,999 mg	271	4,700	1.17 (1.03-1.32)	1.18 (1.04-1.33)
100,000-149,999 mg	395	6,134	1.29 (1.17-1.43)	1.30 (1.17-1.44)
150,000-199,999 mg	329	4,863	1.38 (1.23-1.54)	1.39 (1.24-1.56)
≥ 200,000 mg	391	5,230	1.50 (1.35-1.67)	1.54 (1.38-1.71)
Squamous cell carcinoma				
Non-use	6,817	149,944	1.0 (ref.)	1.0 (ref.)
Ever use	1,812	22,518	1.80 (1.70-1.90)	1.75 (1.66-1.85)
High use	862	4,802	4.05 (3.75-4.39)	3.98 (3.68-4.31)
Cumulative amount				
1-9,999 mg	392	8,369	1.04 (0.93-1.15)	1.01 (0.91-1.12)
10,000-24,999 mg	283	5,476	1.14 (1.01-1.29)	1.12 (0.99-1.27)
25,000-49,999 mg	275	3,871	1.57 (1.38-1.78)	1.54 (1.36-1.75)
50,000-74,999 mg	133	1,432	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	1,104	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)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.

[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

401 **Table 3**

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

Subgroup	Cases Exposed /unexposed	Controls Exposed /unexposed	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
< 50 years	20 / 9,584	215 / 191,556	1.84 (1.16-2.91)	1.91 (1.20-3.03)
50-60 years	156 / 13,130	2,431 / 263,283	1.29 (1.10-1.52)	1.38 (1.17-1.62)
60-75 years	854 / 26,068	13,403 / 522,436	1.27 (1.18-1.36)	1.29 (1.20-1.38)
75+ years	867 / 14,871	14,026 / 304,619	1.27 (1.18-1.37)	1.26 (1.17-1.35)
Male	580 / 30,407	9,308 / 612,587	1.26 (1.15-1.37)	1.26 (1.15-1.37)
Female	1,317 / 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	4,815 / 264,068	1.12 (0.99-1.27)	1.19 (1.05-1.35)
Skin of upper limb	96 / 3,003	1,408 / 60,577	1.38 (1.11-1.70)	1.41 (1.14-1.75)
Skin of lower limb	114 / 2,496	1,513 / 50,153	1.51 (1.24-1.84)	1.55 (1.27-1.89)
Unspecified part of skin	630 / 20,087	9,343 / 405,759	1.37 (1.26-1.49)	1.39 (1.27-1.51)
No use of photosens. drugs	1,259 / 46,042	20,574 / 971,208	1.31 (1.23-1.39)	1.34 (1.26-1.43)
CCI score = 0	1,103 / 48,163	17,284 / 957,511	1.29 (1.21-1.37)	1.28 (1.20-1.37)
No diabetes	1,590 / 60,854	24,502 / 1,208,817	1.30 (1.23-1.37)	1.28 (1.21-1.35)
No psoriasis or atopic dermatitis	1,841 / 61,975	29,299 / 1,253,574	1.27 (1.21-1.34)	1.29 (1.23-1.36)
No actinic keratosis	1,881 / 63,512	29,998 / 1,281,028	1.27 (1.21-1.33)	1.29 (1.22-1.35)
Squamous cell carcinoma				
< 50 years	7 / 258	(n<5)	61.97 (12.81-299.74)	42.85 (8.31-220.84)
50-60 years	44 / 581	123 / 12,595	7.86 (5.48-11.28)	7.61 (5.24-11.04)
60-75 years	282 / 2,429	1,327 / 53,331	4.76 (4.15-5.47)	4.72 (4.10-5.44)
75+ years	529 / 3,549	3,349 / 78,713	3.55 (3.21-3.92)	3.48 (3.15-3.85)
Male	281 / 3,958	1,844 / 84,936	3.32 (2.91-3.79)	3.26 (2.85-3.72)
Female	581 / 2,859	2,958 / 65,008	4.58 (4.15-5.05)	4.46 (4.04-4.94)
Skin of head and neck	292 / 2,964	2,188 / 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 / 1,943	1,306 / 43,949	5.57 (4.86-6.38)	5.42 (4.72-6.23)
No use of photosens. drugs	567 / 5,053	3,380 / 115,858	3.99 (3.62-4.41)	3.96 (3.59-4.38)
CCI score = 0	464 / 4,223	2,618 / 97,620	4.29 (3.83-4.81)	4.19 (3.74-4.70)
No diabetes	727 / 6,338	3,948 / 138,972	4.13 (3.79-4.50)	4.02 (3.68-4.38)
No psoriasis or atopic dermatitis	823 / 6,608	4,679 / 146,952	4.00 (3.69-4.33)	3.94 (3.63-4.27)
No actinic keratosis	839 / 6,762	4,791 / 149,785	3.98 (3.68-4.31)	3.92 (3.62-4.25)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.
[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

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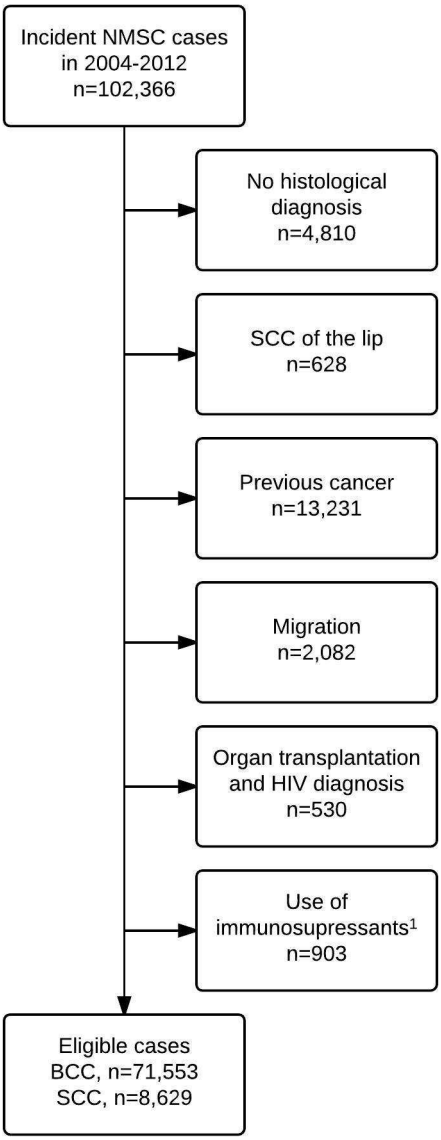

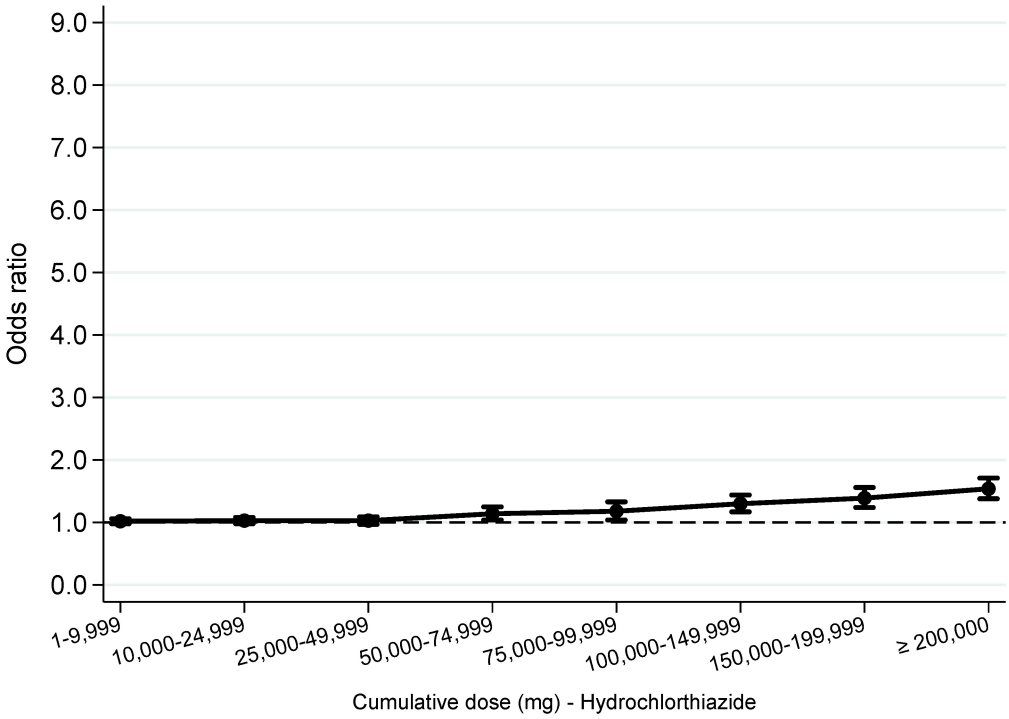

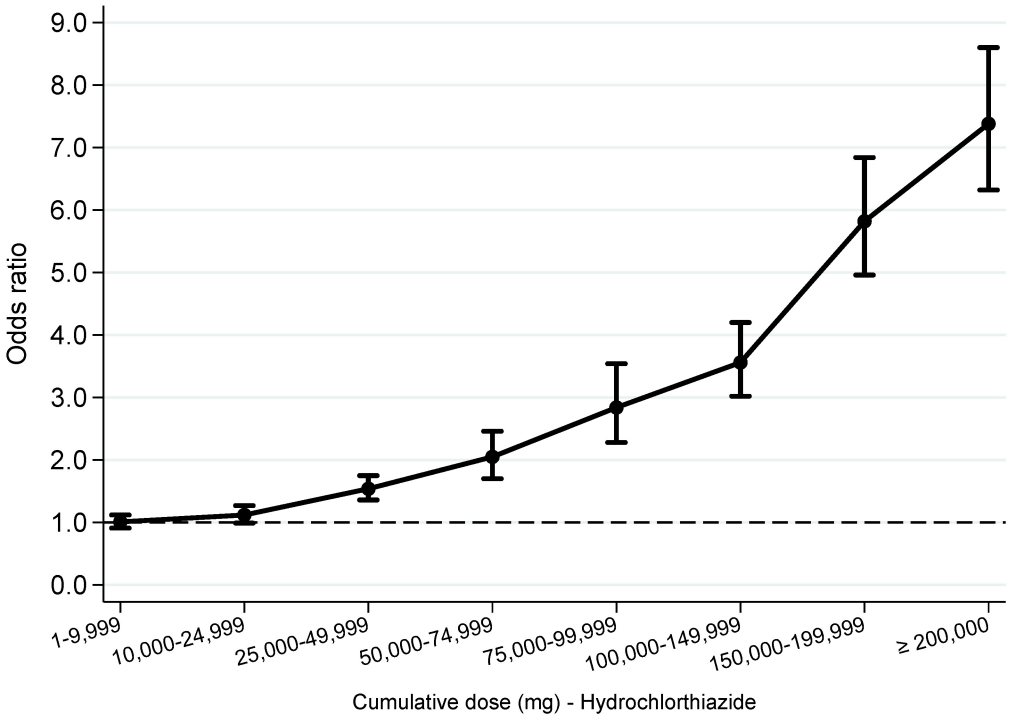

SUPPLEMENTARY MATERIAL

Appendix A – Supplementary and sensitivity analyses

Supplementary Results Ia-g

Association between exposure to bendroflumethiazide, furosemide, calcium-channel blockers, ACE inhibitors, angiotensin II antagonists, indapamide, or nifedipine and risk of NMSC

Supplementary Results II

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

Appendix A – Supplementary 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 ACE inhibitors, ARBs, and CCBs. In the analyses of other diuretics and non-diuretic antihypertensives, associations were adjusted for HCTZ use. In addition, we excluded ever-users of amiloride from the main analyses to obtain risk estimates for BCC and SCC with HCTZ use exclusive of amiloride (primarily preparations of HCTZ and ACE inhibitors or ARBs). Based on the results from the categorical dose-response analyses, the attributable proportion (AP) of HCTZ use for BCC and SCC (assuming causality) was estimated based on adding the single steps in the dose-response analysis together (estimated as AP=(OR – 1) / OR). 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.

Supplementary Results Ia

Association between exposure to bendroflumethiazide and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	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)	4,207	81,884	1.03 (1.00-1.07)	1.06 (1.02-1.09)
Cumulative amount				
1-999 mg	7,130	138,711	1.04 (1.01-1.06)	1.04 (1.01-1.07)
1,000-2,499 mg	3,384	67,970	1.00 (0.97-1.04)	1.02 (0.98-1.06)
2,500-4,999 mg	3,032	60,534	1.01 (0.97-1.05)	1.02 (0.98-1.06)
5,000-7,499 mg	1,770	33,840	1.06 (1.00-1.11)	1.08 (1.02-1.13)
7,500-9,999 mg	1,078	20,815	1.04 (0.98-1.11)	1.07 (1.00-1.14)
≥10,000 mg	1,359	27,229	1.00 (0.95-1.06)	1.03 (0.97-1.09)
Squamous cell carcinoma				
Non-use	5,717	115,881	1.0 (ref.)	1.0 (ref.)
Ever use	2,912	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	1,165	20,507	1.14 (1.07-1.22)	1.09 (1.01-1.16)
1,000-2,499 mg	560	11,079	1.01 (0.92-1.11)	0.99 (0.90-1.09)
2,500-4,999 mg	496	10,326	0.96 (0.87-1.06)	0.97 (0.88-1.07)
5,000-7,499 mg	313	5,962	1.04 (0.92-1.17)	1.06 (0.94-1.20)
7,500-9,999 mg	166	3,786	0.86 (0.73-1.01)	0.92 (0.78-1.09)
≥10,000 mg	212	4,921	0.84 (0.73-0.97)	0.92 (0.79-1.06)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.

[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines,amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

Supplementary Results Ib

Association between exposure to furosemide and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	63,951	1,270,426	1.0 (ref.)	1.0 (ref.)
Ever use	7,602	160,457	0.94 (0.91-0.96)	0.94 (0.92-0.97)
High use (≥2000 DDD)	1,984	43,784	0.90 (0.86-0.94)	0.93 (0.89-0.98)
Cumulative dose (DDD)				
1-399	3,527	71,788	0.97 (0.94-1.01)	0.97 (0.93-1.00)
400-999	1,107	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	9,119	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				
Non-use	6,799	141,645	1.0 (ref.)	1.0 (ref.)
Ever use	1,830	30,817	1.26 (1.19-1.33)	1.11 (1.05-1.18)
High use (≥2000 DDD)	611	9,609	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	4,695	1.11 (0.97-1.26)	0.98 (0.86-1.13)
1000-1999	254	4,475	1.20 (1.05-1.37)	1.07 (0.93-1.23)
2000-2999	169	2,858	1.25 (1.07-1.47)	1.10 (0.93-1.30)
3000-3999	127	1,862	1.42 (1.18-1.71)	1.26 (1.04-1.52)
≥4000	315	4,889	1.36 (1.20-1.53)	1.23 (1.08-1.40)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.
[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

Supplementary Results Ic

Association between exposure to calcium-channel blockers and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	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)	3,630	66,445	1.11 (1.07-1.15)	1.13 (1.09-1.17)
Cumulative dose (DDD)				
1-399	3,321	64,908	1.04 (1.00-1.08)	1.04 (1.00-1.08)
400-999	2,078	39,428	1.06 (1.02-1.11)	1.07 (1.02-1.12)
1000-1999	1,879	37,468	1.02 (0.97-1.07)	1.03 (0.98-1.08)
2000-2999	1,223	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	1,549	27,576	1.14 (1.08-1.20)	1.16 (1.10-1.22)
Squamous cell carcinoma				
Non-use	6,780	138,113	1.0 (ref.)	1.0 (ref.)
Ever use	1,849	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	6,311	1.15 (1.03-1.29)	1.05 (0.94-1.18)
1000-1999	318	6,142	1.05 (0.93-1.18)	0.93 (0.83-1.05)
2000-2999	218	4,006	1.11 (0.96-1.27)	0.97 (0.84-1.12)
3000-3999	143	2,770	1.05 (0.88-1.25)	0.93 (0.78-1.11)
≥4000	266	4,738	1.16 (1.02-1.32)	1.03 (0.90-1.17)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.

[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

Supplementary Results Id

Association between exposure to ACE inhibitors and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	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)	3,889	79,623	0.97 (0.94-1.01)	0.99 (0.96-1.03)
Cumulative dose (DDD)				
1-399	4,632	92,798	0.99 (0.96-1.03)	1.00 (0.96-1.03)
400-999	2,317	47,961	0.96 (0.92-1.01)	0.97 (0.93-1.02)
1000-1999	2,046	43,278	0.94 (0.90-0.99)	0.96 (0.91-1.01)
2000-2999	1,235	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	1,858	37,439	1.00 (0.95-1.05)	1.02 (0.97-1.07)
Squamous cell carcinoma				
Non-use	6,331	130,503	1.0 (ref.)	1.0 (ref.)
Ever use	2,298	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	7,545	1.15 (1.04-1.28)	1.05 (0.95-1.18)
1000-1999	405	6,959	1.20 (1.08-1.34)	1.09 (0.98-1.22)
2000-2999	198	4,203	0.98 (0.85-1.13)	0.87 (0.74-1.01)
3000-3999	164	2,757	1.25 (1.06-1.47)	1.07 (0.91-1.27)
≥4000	373	6,074	1.28 (1.15-1.43)	1.08 (0.96-1.22)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.
[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

46 **Supplementary Results Ie**

47 Association between exposure to angiotensin II receptor antagonists and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	63,470	1,278,247	1.0 (ref.)	1.0 (ref.)
Ever use	8,083	152,636	1.07 (1.04-1.10)	1.06 (1.03-1.09)
High use (≥2000 DDD)	2,659	48,517	1.11 (1.07-1.16)	1.08 (1.03-1.13)
Cumulative dose (DDD)				
1-399	2,086	39,981	1.06 (1.01-1.11)	1.05 (1.00-1.10)
400-999	1,508	29,309	1.04 (0.99-1.10)	1.04 (0.98-1.10)
1000-1999	1,830	34,829	1.06 (1.01-1.12)	1.05 (1.00-1.11)
2000-2999	1,250	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				
Non-use	7,353	149,367	1.0 (ref.)	1.0 (ref.)
Ever use	1,276	23,095	1.13 (1.06-1.20)	0.93 (0.87-1.00)
High use (≥2000 DDD)	457	7,549	1.23 (1.12-1.36)	0.88 (0.79-0.99)
Cumulative dose (DDD)				
1-399	327	5,972	1.10 (0.98-1.24)	0.99 (0.88-1.12)
400-999	231	4,336	1.08 (0.94-1.23)	0.95 (0.82-1.09)
1000-1999	261	5,238	1.01 (0.89-1.15)	0.84 (0.73-0.97)
2000-2999	192	3,542	1.10 (0.94-1.27)	0.82 (0.70-0.97)
3000-3999	136	1,982	1.41 (1.18-1.68)	0.97 (0.81-1.18)
≥4000	129	2,025	1.30 (1.08-1.56)	0.86 (0.71-1.04)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.
[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

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50 **Supplementary Results If**

51 Association between exposure to indapamide and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	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	8,150	0.94 (0.85-1.04)	0.94 (0.85-1.04)
400-999	191	3,584	1.07 (0.92-1.24)	1.07 (0.92-1.24)
1000-1999	97	1,771	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				
Non-use	8,511	170,073	1.0 (ref.)	1.0 (ref.)
Ever use	118	2,389	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	1,324	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	(-)	(-)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.

[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

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Supplementary Results Ig

Association between exposure to nifedipine and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	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	4,206	1.08 (0.95-1.24)	1.08 (0.95-1.24)
Cumulative dose (DDD)				
1-399	514	9,216	1.12 (1.02-1.22)	1.10 (1.01-1.21)
400-999	117	2,339	1.00 (0.83-1.20)	0.99 (0.82-1.20)
1000-1999	131	2,147	1.23 (1.03-1.46)	1.23 (1.03-1.46)
2000-2999	61	1,342	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	1,941	1.17 (0.97-1.42)	1.18 (0.98-1.43)
Squamous cell carcinoma				
Non-use	8,466	169,467	1.0 (ref.)	1.0 (ref.)
Ever use	163	2,995	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	1,416	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)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.
[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

Supplementary Results II

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 [a] (95% CI)	Adjusted OR [b] (95% CI)
Basal cell carcinoma				
Non-use	63,520	1,278,990	1.0 (ref.)	1.0 (ref.)
Ever use	5,033	99,508	1.02 (0.99-1.05)	1.03 (1.00-1.06)
High use (≥50,000 mg)	382	6,457	1.19 (1.07-1.32)	1.21 (1.09-1.34)
Cumulative amount				
1-9,999 mg	2,216	44,331	1.01 (0.97-1.06)	1.02 (0.97-1.06)
10,000-24,999 mg	1,478	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	4,792	1.18 (1.05-1.33)	1.20 (1.06-1.35)
75,000-99,999 mg	74	1,173	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				
Non-use	6,786	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				
1-9,999 mg	285	6,334	1.00 (0.88-1.13)	0.98 (0.87-1.11)
10,000-24,999 mg	213	4,459	1.06 (0.92-1.21)	1.05 (0.91-1.21)
25,000-49,999 mg	175	2,869	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)	(-)	(-)

[a] Adjusted for age, gender, and calendar time by risk-set matching and the conditional analysis.

[b] Fully adjusted model, i.e., additionally adjusted for a) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene; b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or statins; c) history of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease (COPD); d) Charlson Comorbidity Index (CCI) score (0: low; 2: medium; or ≥3: high), and e) highest achieved education (short, medium, long, or unknown).

Capsule summary

What is already known on this topic

Hydrochlorothiazide is photosensitizing and has been linked to lip cancer.

What this article adds to our knowledge

We found a dose-dependent increased risk of non-melanoma skin cancer, particularly squamous cell carcinoma, among users of hydrochlorothiazide.

How this information impacts clinical practice and/or changes patient care

Hydrochlorothiazide use should be carefully considered due to its association with non-melanoma skin cancer.