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 Hølmich, DMSc,e Søren Friis, MD,d,f,g and Anton Pottegård, PhD

Odena, 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.
Nonmelanoma skin cancer (NMSC) is the most common cancer in humans, and the incidence is increasing, particularly among the elderly. 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.

Recently, we reported a strong association between use of the diuretic hydrochlorothiazide (HCTZ) and squamous cell carcinoma (SCC) of the lip. 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 and the recent classification of HCTZ as possibly carcinogenic to humans (group 2B) by the International Agency for Research on Cancer. As HCTZ is among the most widely used drugs in the United States and Western Europe, 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. 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. Therefore, we were interested in examining the association between HCTZ use and NMSC risk more extensively and evaluating the individual effect of HCTZ. 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, the National Prescription Registry, the National Patient Registry, the Danish Education Registers, and the Danish Civil Registration System. 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.

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. 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.

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
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.

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; (2) use of drugs with suggested antineoplastic effects, including aspirin, nonsteroidal anti-inflammatory drugs, and statins; (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); (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 1).

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
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.\textsuperscript{15} Cancer diagnoses obtained from the Cancer Registry were restricted to histologically verified cases, further enhancing validity.\textsuperscript{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.\textsuperscript{23,24} In a recent survey of US dermatologists, patients with multiple SCC tumors reported a frequent history of HCTZ use.\textsuperscript{25} However, only a few observational studies have investigated the association between HCTZ use and NMSC risk.\textsuperscript{10-13} A Dutch study reported no association between

---

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BCC</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>66 (57-76)</td>
<td>66 (57-76)</td>
</tr>
<tr>
<td>Male sex</td>
<td>33,817 (47.3%)</td>
<td>676,286 (47.3%)</td>
</tr>
<tr>
<td>Use of HCTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>63,653 (89.0%)</td>
<td>1,281,894 (89.6%)</td>
</tr>
<tr>
<td>Ever use</td>
<td>7900 (11.0%)</td>
<td>148,989 (10.4%)</td>
</tr>
<tr>
<td>High use</td>
<td>1897 (2.7%)</td>
<td>30,075 (2.1%)</td>
</tr>
<tr>
<td>Use of photosensitizing drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical retinoids</td>
<td>197 (0.3%)</td>
<td>2279 (0.2%)</td>
</tr>
<tr>
<td>Oral retinoids</td>
<td>465 (0.6%)</td>
<td>567 (0.4%)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1563 (2.2%)</td>
<td>23,299 (1.6%)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>16,515 (23.1%)</td>
<td>295,632 (20.7%)</td>
</tr>
<tr>
<td>Aminoquinolines</td>
<td>4405 (6.2%)</td>
<td>70,195 (4.9%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>370 (0.5%)</td>
<td>6106 (0.4%)</td>
</tr>
<tr>
<td>Methoxypsalene</td>
<td>50 (0.1%)</td>
<td>859 (0.1%)</td>
</tr>
<tr>
<td>Other drug use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>14,146 (19.8%)</td>
<td>284,771 (19.9%)</td>
</tr>
<tr>
<td>Nonaspirin NSAID</td>
<td>37,353 (52.2%)</td>
<td>726,091 (50.7%)</td>
</tr>
<tr>
<td>Statins</td>
<td>11,451 (16.0%)</td>
<td>226,657 (15.8%)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>9057 (12.7%)</td>
<td>168,808 (11.8%)</td>
</tr>
<tr>
<td>Diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol-associated conditions</td>
<td>1881 (2.6%)</td>
<td>49,294 (3.4%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3884 (5.4%)</td>
<td>97,388 (6.8%)</td>
</tr>
<tr>
<td>COPD</td>
<td>3093 (4.3%)</td>
<td>66,770 (4.7%)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>581 (0.8%)</td>
<td>12,031 (0.8%)</td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>52,827 (73.8%)</td>
<td>1,045,348 (73.1%)</td>
</tr>
<tr>
<td>1</td>
<td>11,454 (16.0%)</td>
<td>235,072 (16.4%)</td>
</tr>
<tr>
<td>2</td>
<td>4132 (5.8%)</td>
<td>83,546 (5.8%)</td>
</tr>
<tr>
<td>$\geq 3$</td>
<td>3140 (4.4%)</td>
<td>66,917 (4.7%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short, 7-10 y</td>
<td>21,039 (29.4%)</td>
<td>523,901 (36.6%)</td>
</tr>
<tr>
<td>Medium, 11-12 y</td>
<td>27,583 (38.5%)</td>
<td>509,694 (35.6%)</td>
</tr>
<tr>
<td>Long, $\geq 13$ y</td>
<td>18,265 (25.5%)</td>
<td>282,520 (19.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4666 (6.5%)</td>
<td>114,768 (8.0%)</td>
</tr>
</tbody>
</table>

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.
the use of thiazides (including HCTZ) and NMSC risk, whereas a US study found that the use of diuretics overall was significantly associated with an increased risk of BCC. 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 II. Association between exposure to hydrochlorothiazide and risk of NMSC according to cumulative hydrochlorothiazide use

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

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 methoxyspsoralene; (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.
individual thiazides. 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. 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.

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. 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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Case patients exposed/unexposed</th>
<th>Controls exposed/unexposed</th>
<th>Adjusted OR (95% CI)*</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 y</td>
<td>20/9584</td>
<td>215/191,556</td>
<td>1.84 (1.16-2.91)</td>
<td>1.91 (1.20-3.03)</td>
</tr>
<tr>
<td>50-60 y</td>
<td>156/13,130</td>
<td>2431/263,283</td>
<td>1.29 (1.10-1.52)</td>
<td>1.38 (1.17-1.62)</td>
</tr>
<tr>
<td>60-75 y</td>
<td>854/26,068</td>
<td>13,403/522,436</td>
<td>1.27 (1.18-1.36)</td>
<td>1.29 (1.20-1.38)</td>
</tr>
<tr>
<td>≥75 y</td>
<td>867/14,871</td>
<td>14,026/304,619</td>
<td>1.27 (1.18-1.37)</td>
<td>1.26 (1.17-1.35)</td>
</tr>
<tr>
<td>Male</td>
<td>580/30,407</td>
<td>9308/612,587</td>
<td>1.26 (1.15-1.37)</td>
<td>1.26 (1.15-1.37)</td>
</tr>
<tr>
<td>Female</td>
<td>1317/33,246</td>
<td>20,767/669,307</td>
<td>1.28 (1.21-1.36)</td>
<td>1.31 (1.23-1.38)</td>
</tr>
<tr>
<td>Skin of head and neck</td>
<td>783/24,830</td>
<td>12,996/501,337</td>
<td>1.23 (1.14-1.32)</td>
<td>1.22 (1.13-1.31)</td>
</tr>
<tr>
<td>Skin of trunk</td>
<td>274/13,237</td>
<td>4815/264,068</td>
<td>1.12 (0.99-1.27)</td>
<td>1.19 (1.05-1.35)</td>
</tr>
<tr>
<td>Skin of upper limb</td>
<td>96/3003</td>
<td>1408/60,577</td>
<td>1.38 (1.11-1.70)</td>
<td>1.41 (1.14-1.75)</td>
</tr>
<tr>
<td>Skin of lower limb</td>
<td>114/2496</td>
<td>1513/50,153</td>
<td>1.51 (1.24-1.84)</td>
<td>1.57 (1.27-1.89)</td>
</tr>
<tr>
<td>Unspecified part of skin</td>
<td>630/20,087</td>
<td>9348/405,759</td>
<td>1.37 (1.26-1.49)</td>
<td>1.39 (1.27-1.51)</td>
</tr>
<tr>
<td>No use of photosensitizing drugs</td>
<td>1259/46,042</td>
<td>20,574/971,208</td>
<td>1.31 (1.23-1.39)</td>
<td>1.34 (1.26-1.43)</td>
</tr>
<tr>
<td>CCI score of 0</td>
<td>1103/48,163</td>
<td>17,284/957,511</td>
<td>1.29 (1.21-1.37)</td>
<td>1.28 (1.20-1.37)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1590/60,854</td>
<td>24,502/1,208,817</td>
<td>1.30 (1.23-1.37)</td>
<td>1.28 (1.21-1.35)</td>
</tr>
<tr>
<td>No psoriasis or atopic dermatitis</td>
<td>1841/61,975</td>
<td>29,299/1,253,574</td>
<td>1.27 (1.21-1.34)</td>
<td>1.29 (1.23-1.36)</td>
</tr>
<tr>
<td>No actinic keratosis</td>
<td>1881/63,512</td>
<td>29,998/1,281,028</td>
<td>1.27 (1.21-1.33)</td>
<td>1.29 (1.22-1.35)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 y</td>
<td>7/258</td>
<td>(n &lt; 5)</td>
<td>61.97 (12.81-299.74)</td>
<td>42.85 (8.31-220.84)</td>
</tr>
<tr>
<td>50-60 y</td>
<td>44/581</td>
<td>123/12,595</td>
<td>7.86 (5.48-11.28)</td>
<td>7.61 (5.24-11.04)</td>
</tr>
<tr>
<td>60-75 y</td>
<td>282/2429</td>
<td>1327/53,331</td>
<td>4.76 (4.15-5.47)</td>
<td>4.72 (4.10-5.44)</td>
</tr>
<tr>
<td>≥75 y</td>
<td>529/3549</td>
<td>3349/78,713</td>
<td>3.55 (3.21-3.92)</td>
<td>3.48 (3.15-3.85)</td>
</tr>
<tr>
<td>Male</td>
<td>281/3958</td>
<td>1844/84,936</td>
<td>3.32 (2.91-3.79)</td>
<td>3.26 (2.85-3.72)</td>
</tr>
<tr>
<td>Female</td>
<td>581/2859</td>
<td>2958/65,008</td>
<td>4.58 (4.15-5.05)</td>
<td>4.46 (4.04-4.94)</td>
</tr>
<tr>
<td>Skin of head and neck</td>
<td>292/2964</td>
<td>2188/64,025</td>
<td>2.92 (2.56-3.33)</td>
<td>2.83 (2.48-3.23)</td>
</tr>
<tr>
<td>Skin of trunk</td>
<td>46/632</td>
<td>345/13,429</td>
<td>2.93 (2.12-4.06)</td>
<td>2.95 (2.11-4.12)</td>
</tr>
<tr>
<td>Skin of upper limb</td>
<td>112/796</td>
<td>541/17,426</td>
<td>4.70 (3.76-5.87)</td>
<td>4.90 (3.90-6.16)</td>
</tr>
<tr>
<td>Skin of lower limb</td>
<td>101/482</td>
<td>422/11,115</td>
<td>5.80 (4.54-7.41)</td>
<td>5.88 (4.57-7.56)</td>
</tr>
<tr>
<td>Unspecified part of skin</td>
<td>311/1943</td>
<td>1306/43,949</td>
<td>5.57 (4.86-6.38)</td>
<td>5.42 (4.72-6.23)</td>
</tr>
<tr>
<td>No use of photosensitizing drugs</td>
<td>567/5053</td>
<td>3380/115,858</td>
<td>3.99 (3.62-4.41)</td>
<td>3.96 (3.59-4.38)</td>
</tr>
<tr>
<td>CCI score of 0</td>
<td>464/4223</td>
<td>2618/97,620</td>
<td>4.29 (3.83-4.81)</td>
<td>4.19 (3.74-4.70)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>727/6338</td>
<td>3948/138,972</td>
<td>4.13 (3.79-4.50)</td>
<td>4.02 (3.68-4.38)</td>
</tr>
<tr>
<td>No psoriasis or atopic dermatitis</td>
<td>823/6608</td>
<td>4679/146,952</td>
<td>4.00 (3.69-4.33)</td>
<td>3.94 (3.63-4.27)</td>
</tr>
<tr>
<td>No actinic keratosis</td>
<td>839/6762</td>
<td>4791/149,785</td>
<td>3.98 (3.68-4.31)</td>
<td>3.92 (3.62-4.25)</td>
</tr>
</tbody>
</table>

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, aminquinolines, 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).
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.\(^{30}\) 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.

Chris B. Jakobsen (the Danish Medicine Agency) is acknowledged for his valuable help identifying the HCTZ content of combination products that are no longer marketed in Denmark. Morten Olesen and Martin Thomsen Ernst (University of Southern Denmark) are acknowledged for their help with data management.

REFERENCES


SUPPLEMENTAL AND SENSITIVITY ANALYSES

First, we repeated the main analyses for other diuretic drugs with suggested photosensitizing properties, including bendroflumethiazide and furosemide.\textsuperscript{10,12,13} Next, we performed analyses for other antihypertensives, including angiotensin-converting enzyme inhibitors, angiotensin 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 angiotensin 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

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

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.
1Fully 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 $\geq$3, high); and (5) highest achieved education (short, medium, long, or unknown).
### Supplemental Table II. Association between exposure to furosemide and risk of NMSC

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

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, aminoguinalines, 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

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

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

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

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

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

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.

1Fully 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

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

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, aminquinolines, 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

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

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

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

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.

1Fully adjusted model, that is, additionally adjusted for (1) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminosteroids, 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) Charlon comorbidity index score (0: low; 2: medium; or ≥3: high); and (5) highest achieved education (short, medium, long, or unknown).