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Abstract. Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, Friis S (University of Southern Denmark; Odense University Hospital, Odense; Kaiser Permanente Northern California, Oakland, CA, USA; Danish Cancer Society, Copenhagen, Denmark). Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med* 2017; **282**: 322–331.

Background. The diuretic hydrochlorothiazide is amongst the most frequently prescribed drugs in the United States and Western Europe, but there is suggestive evidence that hydrochlorothiazide use increases the risk of lip cancer.

Objectives. To study the association between use of hydrochlorothiazide and squamous cell carcinoma of the lip.

Methods. We conducted a case–control study using Danish nationwide registry data. From the Cancer Registry (2004–2012), we identified 633 case patients with squamous cell carcinoma (SCC) of the lip and matched them to 63 067 population controls using a risk-set sampling strategy. Hydrochlorothiazide use (1995–2012) was obtained from the Prescription Registry and defined according to cumulative use. Applying conditional logistic regression, we calculated odds ratios (ORs) for SCC lip cancer associated with hydrochlorothiazide use, adjusting for predefined potential confounders obtained from demographic, prescription and patient registries.

Results. Ever-use of hydrochlorothiazide was associated with an adjusted OR for SCC lip cancer of 2.1 (95% confidence interval (CI): 1.7–2.6), increasing to 3.9 (95%CI: 3.0–4.9) for high use (≥25 000 mg). There was a clear dose–response effect ($P < 0.001$), with the highest cumulative dose category of hydrochlorothiazide (≥100 000 mg) presenting an OR of 7.7 (95%CI: 5.7–10.5). No association with lip cancer was seen with use of other diuretics or nondiuretic antihypertensives. Assuming causality, we estimated that 11% of the SCC lip cancer cases could be attributed to hydrochlorothiazide use.

Conclusions. Hydrochlorothiazide use is strongly associated with an increased risk of lip cancer.

Keywords: cancer, epidemiology, hydrochlorothiazide, pharmacology.

Introduction

The diuretic hydrochlorothiazide (HCTZ) is amongst the most frequently prescribed drugs in the United States (US) and Western Europe [1, 2]. In the United States alone, more than 10 million patients annually use HCTZ [2]. It has primarily been employed as a first-line treatment for hypertension, often in combination with other antihypertensive drugs, but is also used for oedema and congestive heart failure.

In a screening study from 2009, Friedman and colleagues performed an exploratory study, identifying a potential association between HCTZ and lip cancer [3]. This signal was later refined in a tailored analysis, suggesting a fourfold increased lip cancer risk with ≥5 years of HCTZ use [4]. Sun exposure is the predominant risk factor for lip cancer, and the photosensitizing properties of HCTZ [5] could explain its link to lip cancer. In 2013, the International Agency for Research on Cancer (IARC) classified HCTZ as ‘possibly carcinogenic to humans’ (Group 2B) [6], based partially on the lip cancer findings [4] and accumulating laboratory and epidemiologic evidence linking drug-induced photosensitivity to skin cancer [7–9].

We recently reported the results of a screening study of drug–cancer associations [10]. Herein, we observed an association between use of a combined preparation of HCTZ and amiloride and increased risk of squamous cell carcinoma (SCC) of the lip. This finding, together with the sparse epidemiologic evidence of an association between HCTZ use and lip cancer [4] and the request for further studies of drugs classified as potentially carcinogenic by the IARC [11], prompted us to conduct more extensive analyses of the association between HCTZ use and risk of SCC lip cancer using detailed data from the Danish nationwide registries.

Materials and methods

We conducted a nested case–control analysis of nationwide registry data comparing HCTZ use amongst patients diagnosed with SCC of the lip (cases) with use amongst cancer-free persons (controls) to estimate odds ratios (ORs) for SCC lip cancer associated with HCTZ use. We obtained data from five nationwide registry sources: the Danish Cancer Registry [12], Danish National Prescription Registry [13], Danish National Patient Registry [14], Danish Education Registries [15] and Danish Civil Registration System [16, 17]. The Supplementary Material provides a detailed description of the registries (Appendix S1) with codes for tumour characteristics, drug exposure and covariates (Appendix S2).

Case selection

Cases were all Danish residents with a biopsy-verified first diagnosis of SCC of the lip between 1 January 2004 and 31 December 2012. Cases had no history of cancer (except nonmelanoma skin cancer) prior to the lip cancer diagnosis (index date), were continuous residents in Denmark for at least 10 years prior to the index date and had no record of organ transplantation, azathioprine use or diagnoses of HIV or AIDS (because of the association between immunosuppression and skin cancer) [18–21].

Control selection

For each case, using a risk-set sampling strategy, we selected 100 controls amongst all Danish residents matched by sex and birth year, applying the same exclusion criteria as for cases. The index dates used for controls were identical to the dates of the corresponding cases. Persons were eligible as controls before they became cases. Therefore, the calculated ORs provide unbiased estimates of the incidence rate ratios that would have emerged from a cohort study based on the source population [22].

Exposure assessment

Ever-use of HCTZ was defined as having filled at least one prescription for a HCTZ-containing drug prior to the index date; never-use was defined as no such prescriptions. In Denmark, HCTZ is prescribed almost exclusively in combination preparations with nondiuretic antihypertensives or with the potassium-sparing diuretic amiloride. We defined high use of HCTZ as filled prescriptions equivalent to ≥25 000 mg of HCTZ, corresponding to approximately 3 years of cumulative use (1000 defined daily doses [23]).

Prescriptions filled within 2 years before the index date (lag-time) were disregarded to allow a reasonable induction period for an effect on lip cancer risk and to guard against the possibility that increased medical attention before the cancer diagnosis influenced prescribing of HCTZ, introducing 'reverse causation' [24]. In sensitivity analyses, we varied the length of the lag-time.

Analytical variables

We based potential confounder selection on data available in nationwide prescription, patient and education registries: (i) use of selected drugs with suggested photosensitizing properties, including oral retinoids, topical retinoids, tetracycline, macrolides, aminoquinolines and amiodarone [9, 25–27]; (ii) use of drugs with suggested cancer chemopreventive effects, including aspirin, nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and statins [11]; (iii) history of diabetes, chronic obstructive pulmonary disease (COPD) and conditions associated with heavy alcohol consumption, derived from composite measures of hospital diagnoses and prescription use of disease-specific drugs (see Appendix S2); (iv) history of nonmelanoma skin cancer; (v) average Charlson Comorbidity Index (CCI) scores [28, 29] (0 low; 1–2: medium; or ≥3: high), derived from diagnoses of 19 chronic conditions; and (vi) highest achieved education (short; medium; higher; unknown) as a measure of socio-economic status. Exposure to each potential confounder drug was defined as two or more prescriptions on separate dates, and hospital histories of each of the selected conditions were defined as a primary or secondary discharge or ambulatory diagnosis. As for HCTZ use, we disregarded covariate information recorded less than 2 years prior to the index date.

Main analyses

The analysis followed a conventional matched case–control approach. We computed the frequency and proportion of cases and controls within categories of the exposure and covariates. Using conditional logistic regression analysis, we computed ORs with 95% confidence intervals (CIs) for SCC lip cancer associated with HCTZ use whilst adjusting for the predefined potential confounders. The effect of age and sex was handled by the matching and conditional analysis. Additionally, to examine a potential dose–response relationship, we performed analyses stratified according to predefined categories of cumulative HCTZ use. A formal dose–response analysis was performed by restricting analyses to ever-users and estimating the incremental OR for each 25 000 mg HCTZ (capping exposure at 100 000 mg), using ordinary logistic regression whilst also adjusting for sex and age as a continuous variable. Never-use served as the reference group for all analyses unless stated otherwise.

To estimate the proportion of SCC lip cancer cases that, during our study period, could be attributed to use of HCTZ, we calculated the 'population-level attributable proportion' (AP_{pop}) using the following equation: $AP_{pop} = prop_{cases} \cdot (OR\text{-}1)/OR$. Here, $prop_{cases}$ denotes the proportion of all SCC lip cancer cases classified as exposed to high use of HCTZ. The applied OR was that obtained for the main analysis, that is the fully adjusted association between high use of HCTZ and SCC lip cancer.

Secondary and sensitivity analyses

We performed a number of preplanned subanalyses. First, we defined HCTZ use according to duration and intensity of use, assuming that the number of tablets represented the number of days that HCTZ was taken (whilst not allowing stockpiling). For intensity of use, we estimated the average daily dose of HCTZ as the total amount of drug filled (summing defined daily doses) divided by the estimated cumulative duration of use. Secondly, we performed subgroup analyses according to age and sex or with restriction to specific subsets of the study population: never-user of other photosensitizing drugs (as defined above); low comorbidity (CCI score = 0); no history of diabetes; or no history of nonmelanoma skin cancer. Thirdly, we repeated the main analyses for bendroflumethiazide, besides HCTZ the most frequently prescribed thiazide in Denmark, and for the loop diuretic furosemide that has been suggested to possess photosensitizing properties [9, 25–27]. In dose–response analyses of bendroflumethiazide, we used dose categories that were 10 times lower than for HCTZ because bendroflumethiazide is considered to be about 10 times as potent [30, 31]. We also performed analyses for antihypertensives with similar indications to thiazides (that is primarily mild to moderate hypertension), including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II (ATII) antagonists and group 2 calcium-channel blockers (CCBs). Amongst CCBs, we excluded nifedipine that possesses photosensitizing properties and has been associated with an increased risk of lip cancer [4]. In Denmark, however, nifedipine prescriptions only comprise only 1.8% of the total sales of CCBs [32], precluding meaningful analyses of this drug. In analyses of other diuretics and nondiuretic antihypertensives, associations were adjusted for HCTZ use. Fourthly, we restricted HCTZ use to combination therapy with amiloride, which generated the 'drug–cancer signal' with lip cancer in our recent screening study [10]. Fifthly, we excluded ever-users of amiloride from the main analyses to obtain ORs for SCC lip cancer associated with HCTZ use exclusive of amiloride use. Finally, we repeated the main analyses varying the lag-time between 0 and 5 years (in steps of 6 months).

Other

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

Results

Main analysis

After exclusions (*n* = 222), the study population comprised 633 biopsy-verified SCC cases (Fig. 1) matched to 63 067 cancer-free controls. Cases had higher comorbidity and lower educational status than controls (Table 1). The remaining characteristics were similar amongst cases and controls.

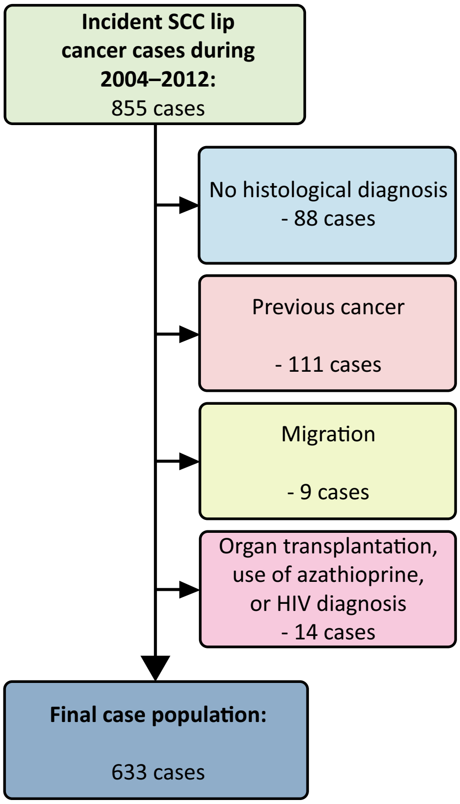

Fig. 1 *Flow chart of case selection.*

Hydrochlorothiazide was obtained mainly in combination with ATII antagonists (44% of all prescriptions filled amongst controls), amiloride (33%) and ACE inhibitors (21%). Overall, 14.8% of cases and 4.4% of controls were high-users (≥25 000 mg) of HCTZ, yielding an adjusted OR for SCC lip cancer of 3.9 (95%CI: 3.0–4.9). Analyses defining HCTZ use according to cumulative amount showed a clear dose–response pattern, with high ORs in both the predefined (≥50 000 mg: 5.5; 95%CI: 4.2–7.2) and *post hoc* (≥100 000 mg: 7.7; 95%CI: 5.7–10.5) upper exposure categories (Table 2). In the dose–response analysis, the incremental OR per 25 000 mg HCTZ was 1.7 (95%CI: 1.5–1.9, $P < 0.001$). Analyses defining HCTZ use according to duration or intensity also revealed clear trends towards higher values in the upper exposure categories (duration ≥5 years: OR, 4.5; 95%CI: 3.5–5.9; intensity ≥32.25 mg day^{-1}: OR, 4.9; 95% CI: 3.0–7.8) (Table 3). The estimation of the 'population-level attributable proportion' (AP_{pop}) yielded a value of 0.11; equivalent to 11% of all SCC lip cancer cases occurring during the study period could be attributed to high use of HCTZ (assuming causality).

Table 1 *Characteristics of lip cancer cases and matched controls*

	Cases (n = 633)	Controls (n = 63 067)
Age, median (IQR)	72 (64–80)	72 (64–80)
Male	426 (67.3%)	42 499 (67.4%)
Use of HCTZ		
Never-use	494 (78.0%)	55 666 (88.3%)
Ever-use	139 (22.0%)	7401 (11.7%)
High use	94 (14.8%)	2771 (4.4%)
Use of photosensitizing drugs		
Any	309 (48.8%)	27 819 (44.1%)
Topical retinoids	12 (1.9%)	1183 (1.9%)
Oral retinoids	5 (0.8%)	1255 (2.0%)
Tetracycline	29 (4.6%)	3084 (4.9%)
Macrolides	269 (42.5%)	23 729 (37.6%)
Aminoquinolines	114 (18.0%)	9581 (15.2%)
Amiodarone	7 (1.1%)	1596 (2.5%)
Other drug use		
Aspirin	185 (29.2%)	17 881 (28.4%)
Nonaspirin NSAIDs	340 (53.7%)	32 610 (51.7%)
Statins	136 (21.5%)	12 888 (20.4%)
Diagnoses		
Alcohol-associated conditions	28 (4.4%)	2128 (3.4%)
Diabetes	66 (10.4%)	5116 (8.1%)
COPD	47 (7.4%)	3675 (5.8%)
CCI score		
0	374 (59.1%)	41 872 (66.4%)
1	138 (21.8%)	11 835 (18.8%)
2	58 (9.2%)	5044 (8.0%)
≥3	63 (10.0%)	4316 (6.8%)
Education		
Short	321 (50.7%)	24 431 (38.7%)
Medium	171 (27.0%)	21 796 (34.6%)
Long	75 (11.8%)	10 882 (17.3%)
Unknown	66 (10.4%)	5958 (9.4%)

HCTZ, hydrochlorothiazide; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index.

Table 2 *Association between exposure to hydrochlorothiazide and risk of squamous cell carcinoma of the lip, according to cumulative amount of hydrochlorothiazide use*

Subgroup	Cases	Controls	Crude OR[a]	Adjusted OR[b]
Nonuse	494	55 666	1.0 (ref.)	1.0 (ref.)
Ever-use	139	7401	2.2 (1.8–2.6)	2.1 (1.7–2.6)
High use (≥25 000 mg)	94	2771	4.0 (3.2–5.0)	3.9 (3.0–4.9)
Cumulative amount				
1–4999 mg	16	1745	1.0 (0.6–1.7)	1.0 (0.6–1.7)
5000–9999 mg	12	1083	1.2 (0.7–2.2)	1.2 (0.7–2.2)
10 000–24 999 mg	17	1802	1.1 (0.7–1.7)	1.1 (0.7–1.7)
25 000–49 999 mg	20	1253	1.9 (1.2–2.9)	1.8 (1.2–2.9)
≥50 000 mg	74	1518	5.8 (4.5–7.5)	5.5 (4.2–7.2)
Post hoc categories[c]				
50 000–74 999 mg	12	460	3.0 (1.7–5.4)	2.9 (1.6–5.3)
75 000–99 999 mg	8	254	3.7 (1.8–7.5)	3.4 (1.7–7.0)
≥100 000 mg	54	804	8.2 (6.1–11.1)	7.7 (5.7–10.5)

[a]Adjusted for age, gender and calendar time (by risk-set matching and conditional analysis). [b]Fully adjusted model, additionally adjusted for (i) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines and amiodarone; (ii) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs or statins; (iii) history of heavy alcohol consumption, diabetes or chronic obstructive pulmonary disease; (iv) history of nonmelanoma skin cancer; (v) Charlson Comorbidity Index score (0: low; 1–2: medium; or ≥3: high); and (vi) highest achieved education (short, medium, long or unknown). [c]Performed as post hoc analyses due to the unexpectedly large number of cases in the highest of the predefined exposure categories (≥50 000 mg).

Secondary and sensitivity analyses

In secondary analyses of high-use HCTZ, only minor variations in ORs were seen according to age or sex or within the selected subgroups of study subjects (Table 4). In general, the adjustment for potential confounders had limited influence on the OR estimates (Table S1).

In analyses of bendroflumethiazide or CCB use, we found no apparent associations with SCC lip cancer risk, overall or according to cumulative amount, duration or intensity of use (Table 5). Similarly, we observed no associations for SCC lip cancer with use of ACE inhibitors, ATII antagonists or furosemide (Table S2a–c).

Individual analyses of amiloride was not feasible, because almost all (>99%) amiloride was prescribed in combination with HCTZ. Excluding ever-users of amiloride, we observed a dose–response pattern for HCTZ use similar to the main analysis, that is a neutral OR for SCC lip cancer with a cumulative amount <25 000 mg (ORs 1.0–1.1), increasing to ORs of 1.7 (95%CI: 1.0–2.9) and 2.4 (95%CI: 1.0–5.8) for 25 000–49 000 mg and 50 000–74 999 mg, respectively. We could not estimate associations for a cumulative amount above 75 000 mg, as subjects with highest use of HCTZ had predominantly used the HCTZ–amiloride combination.

In analyses varying the lag-time prior to the index date, we found increasing ORs for SCC lip cancer with increasing lag-time for HCTZ exposure, from 3.1 (95%CI: 2.5–3.9) with no lag-time to 5.3 (95% CI: 4.1–6.7) with 5 years of lag-time (Table S3). The (null) association between bendroflumethiazide use and SCC lip cancer risk did not vary according to length of lag-time (data not shown).

Discussion

In this nationwide case–control study, use of the photosensitizing diuretic HCTZ was associated with a substantially increased risk of SCC of the lip. Risk increased with increasing cumulative amount, duration and intensity of HCTZ use. More than 100 000 mg of HCTZ, corresponding to more than 10 years of cumulative use, was associated with a sevenfold increased risk for SCC lip cancer. Assuming causality, an estimated 11% of all SCC lip cancer cases occurring the study period could

Table 3 *Association between exposure to hydrochlorothiazide and risk of squamous cell carcinoma of the lip, according to cumulative duration and intensity of hydrochlorothiazide use*

Subgroup	Cases	Controls	Crude OR[a]	Adjusted OR[b]
Nonuse	494	55 666	1.0 (ref.)	1.0 (ref.)
Cumulative duration of use[c]				
0–1 year	22	2365	1.1 (0.7–1.6)	1.0 (0.7–1.6)
1–2 years	13	1091	1.3 (0.7–2.3)	1.3 (0.7–2.2)
2–3 years	5	821	0.7 (0.3–1.7)	0.7 (0.3–1.7)
3–5 years	25	1256	2.3 (1.5–3.5)	2.3 (1.5–3.4)
5+ years	74	1868	4.7 (3.6–6.0)	4.5 (3.5–5.9)
Intensity of use amongst high-users[d]				
6.25 mg day^{-1}	(n < 5)	(n < 5)	(-)	(-)
12.5 mg day^{-1}	13	672	2.3 (1.3–4.0)	2.3 (1.3–4.0)
18.75 mg day^{-1}	5	153	4.0 (1.6–9.9)	3.8 (1.5–9.5)
25 mg day^{-1}	44	745	7.0 (5.1–9.8)	6.7 (4.8–9.3)
≥32.25 mg da^{-1}y	20	448	5.4 (3.4–8.5)	4.9 (3.0–7.8)

[a]Adjusted for age, gender and calendar time (by risk-set matching and conditional analysis). [b]Fully adjusted model, additionally adjusted for (i) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines and amiodarone; (ii) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs or statins; (iii) history of heavy alcohol consumption, diabetes or chronic obstructive pulmonary disease; (iv) history of nonmelanoma skin cancer; (v) Charlson Comorbidity Index score (0: low; 1–2: medium; or ≥3: high); and (vi) highest achieved education (short, medium, long or unknown). [c]The duration of use assigned to each prescription was estimated assuming an intake of one tablet daily whilst not allowing stockpiling. [d]Restricted to those with high use of hydrochlorothiazide (≥25 000 mg). Intensity of use was estimated by dividing the total amount of drug filled with the estimated cumulative duration of use, whilst rounding to the nearest value of the categories.

be attributed to use of HCTZ. Meanwhile, use of the diuretics bendroflumethiazide or furosemide or nondiuretic antihypertensive drugs was not associated with increased lip cancer risk.

The strengths of our study are its national scale and large population, long study period and high-quality registry data with lip cancer diagnoses restricted to histologically verified SCC cases identified from the Danish Cancer Registry, which is known to have accurate and virtually complete registration of incident cancers in Denmark [12]. The use of the Danish Prescription Registry also ensured complete and high-quality assessment of drug use with up to 18 years of exposure history [13]. The main limitation was lack of information on UV exposure and tobacco smoking, the two major risk factors for lip cancer. However, we find it unlikely that HCTZ users would have markedly different sun exposure or smoking patterns than never-users. To reduce partially potential confounding by tobacco smoking, we adjusted for COPD as a crude measure of heavy smoking. We also adjusted for both individual chronic diseases and general comorbidity, estimated by average CCI scores. Differences in comorbidity might introduce bias if medical attention and thus diagnostic opportunity for lip cancer were higher amongst HCTZ users because of higher comorbidity than amongst never-users of HCTZ. However, such surveillance bias is unlikely to occur specifically amongst HCTZ users and not amongst users of other antihypertensive drugs. Notwithstanding the possibility of residual confounding by sun exposure or tobacco smoking, differences in these risk factors according to HCTZ use would need to be extremely large to account for the up to sevenfold increased ORs observed in our study.

Our findings are compatible with the results reported by Friedman *et al.* who found that ≥5 years of cumulative HCTZ use was associated with an OR for lip cancer of 4.22 (95%CI: 2.82–6.31) [4]. The authors observed similar results for HCTZ monotherapy. We could not evaluate association for HCTZ monotherapy, because in Denmark nearly all HCTZ was prescribed as a combination preparation with amiloride or with nondiuretic

Table 4 *Associations between high use of hydrochlorothiazide (≥25 000 mg) and risk of squamous cell carcinoma of the lip, according to patient subgroups*

Subgroup	Cases exposed / unexposed	Controls exposed / unexposed	Crude OR[a]	Adjusted OR[b]
Age group				
<60 years	8/81	131/8943	7.4 (3.4–16.0)	6.7 (2.9–15.1)
60–75 years	34/239	1141/25 561	3.2 (2.2–4.7)	3.2 (2.2–4.7)
75+ years	52/174	1499/21 162	4.3 (3.1–5.9)	4.2 (3.0–5.9)
Gender				
Male	39/356	1507/38 008	2.8 (2.0–4.0)	2.9 (2.0–4.0)
Female	55/138	1264/17 658	5.8 (4.2–8.1)	5.4 (3.9–7.6)
Other				
No use of photosensitizing drugs[c]	40/260	1298/31 598	4.1 (2.9–5.8)	4.2 (2.9–6.1)
No previous NMSC	91/478	2701/54 806	4.0 (3.2–5.1)	3.9 (3.1–5.0)
CCI score = 0	53/297	1461/37 843	4.8 (3.6–6.6)	4.5 (3.3–6.3)
No diabetics	81/448	2232/51 810	4.3 (3.4–5.6)	4.2 (3.3–5.5)

CCI, Charlson comorbidity index; NMSC, nonmelanoma skin cancer; [a]Adjusted for age, gender and calendar time (by risk-set matching and conditional analysis). [b]Fully adjusted model, additionally adjusted for (i) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines and amiodarone; (ii) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs or statins; (iii) history of heavy alcohol consumption, diabetes or chronic obstructive pulmonary disease; (iv) history of nonmelanoma skin cancer; (v) CCI score (0: low; 1–2: medium; or ≥3: high); and (vi) highest achieved education (short, medium, long or unknown). [c]This included oral retinoids, topical retinoids, tetracycline, macrolides, aminoquinolines and amiodarone.

antihypertensives. Theoretically, amiloride use could have contributed to the increased risk observed with overall use of HCTZ, but current evidence rather suggests that amiloride may possess antineoplastic effects [33]. Furthermore, a similar dose–response pattern for HCTZ was observed in our study when use of amiloride was excluded. To our knowledge, the association between HCTZ use and lip cancer risk has hitherto only been specifically addressed in the study by Friedman *et al.* [4]. However, several epidemiological studies of various photosensitizing diuretics, including HCTZ, have indicated that HCTZ use may increase skin cancer risk [6, 8, 9, 26, 27, 34], notably for SCC, but results are inconsistent [6, 9]. HCTZ use was common in a US case series of patients with a history of multiple SCCs [35], and experimental data support a carcinogenic potential of HCTZ [5–7]. The hypothesis is that HCTZ and other drugs with photosensitizing properties may influence cancer risk at sun-exposed sites and may also induce a chronic inflammatory reaction [5, 6].

We found no association between bendroflumethiazide use and lip cancer risk, even with high cumulative use. An explanation for this seemingly inconsistent risk pattern for photosensitizing drugs within the same chemical class [23] would be that the photosensitizing effect varies with the molar concentrations of the drug independently of its diuretic action. In cell and mouse models, bendroflumethiazide has similar photosensitizing properties as HCTZ at equimolar concentrations [30, 31]. However, bendroflumethiazide is a much more potent diuretic and is typically used at 10 times lower doses and has a threefold shorter half-life [36, 37], thus resulting in an overall 30-fold lower molar concentration at therapeutically equivalent doses.

Conclusion

We found a strong association between HCTZ use and SCC of the lip. The high odds ratios, evidence of specificity for HCTZ use compared to use of other

Table 5 *Association between exposure to bendroflumethiazide or calcium-channel blockers and risk of squamous cell carcinoma of the lip, according to cumulative amount of use*

Subgroup	Cases	Controls	Crude OR[a]	Adjusted OR[b]
Bendroflumethiazide[c]				
Nonuse	449	45 763	1.0 (ref.)	1.0 (ref.)
Ever-use	184	17 304	1.1 (0.9–1.3)	1.0 (0.8–1.2)
Long-term use (≥2500 mg)	71	7262	1.0 (0.8–1.3)	1.0 (0.8–1.3)
Cumulative amount				
1–499 mg	50	4341	1.2 (0.9–1.6)	1.1 (0.8–1.5)
500–999 mg	27	2273	1.2 (0.8–1.8)	1.1 (0.8–1.7)
1000–2499 mg	36	3428	1.1 (0.7–1.5)	1.0 (0.7–1.4)
2500–4999 mg	29	3148	0.9 (0.6–1.4)	0.9 (0.6–1.4)
≥5000 mg	42	4114	1.0 (0.7–1.5)	1.1 (0.8–1.5)
Group 2 calcium-channel blockers, excluding nifedipine[d]				
Nonuse	496	51 915	1.0 (ref.)	1.0 (ref.)
Ever-use	137	11 152	1.3 (1.1–1.6)	1.1 (0.9–1.4)
Long-term use (≥1000 DDD)	70	5714	1.3 (1.0–1.7)	1.1 (0.8–1.5)
Cumulative amount				
1–199 DDD	24	2092	1.2 (0.8–1.9)	1.0 (0.7–1.5)
200–399 DDD	14	1249	1.3 (0.7–2.1)	1.0 (0.6–1.7)
400–999 DDD	29	2097	1.4 (1.0–2.1)	1.2 (0.8–1.7)
1000–1999 DDD	19	1928	1.1 (0.7–1.7)	0.9 (0.6–1.4)
≥2000 DDD	51	3786	1.5 (1.1–2.0)	1.2 (0.9–1.6)

DDD, defined daily doses. [a]Adjusted for age, gender and calendar time (by risk-set matching and conditional analysis). [b]Fully adjusted model, additionally adjusted for (i) use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines and amiodarone; (ii) aspirin, nonaspirin nonsteroidal anti-inflammatory drugs or statins; (iii) history of heavy alcohol consumption, diabetes or chronic obstructive pulmonary disease; (iv) history of nonmelanoma skin cancer; (v) Charlson Comorbidity Index score (0: low; 1–2: medium; or ≥3: high); (vi) highest achieved education (short, medium, long or unknown); and (vii) use of hydrochlorothiazide. [c]2.5 mg of bendroflumethiazide is equivalent to 25 mg of hydrochlorothiazide. [d]Use of calcium-channel blockers was estimated in DDD as an aggregate measure of exposure to different calcium-channel blockers. One DDD is equivalent to, for example, 5 mg of amlodipine, 5 mg of felodipine and 10 mg of lercanidipine (see www.whocc.no/atc_ddd_index).

diuretics or nondiuretic antihypertensives, and the plausible biological mechanism of photosensitivity support a causal relationship between HCTZ use and risk of lip cancer. Given the considerable use of HCTZ worldwide, such numbers and attributable proportions are not negligible when drugs comparable in indications and efficacy to HCTZ are available.

Conflicts of interest statement

Anton Pottegård, Jesper Hallas and Mathias T. Svendsen have participated in research projects, unrelated to the present study, using grants provided by LEO Pharma (manufacturer of bendroflumethiazide) to the institution where the authors were employed. The remaining authors declare no conflict of interests. The work was funded by the Danish Council for Independent Research [4004-00234B]. The funding source had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Effect of confounder adjustment.

Table S2. ACE inhibitors, ATII antagonists and furosemide and risk of squamous cell carcinoma.

Table S3. Effect of lag-time.

Appendix S1. Danish Nationwide Health Registries.

Appendix S2. Codes and definitions.

