ORIGINAL ARTICLE

Association between hydrochlorothiazide exposure and different incident skin, lip and oral cavity cancers: A series of population-based nested case–control studies

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Aims: Hydrochlorothiazide-induced photosensitivity may increase squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and lip cancer risk. The aim was to quantify these risks.

Methods: Nested case–control studies using data from the UK THIN database from 01 January 1999 to 01 May 2016. Adults with incident SCC, BCC, melanoma, lip cancer and oral cancer were matched (on age, sex and calendar year of cohort entry) to controls using incidence density sampling. Incidence rate ratios (IRR) for each outcome were calculated for ever and cumulative hydrochlorothiazide exposure, measuring the impact of additionally adjusting for smoking and body mass index (BMI). Adjusted rate differences were estimated, including the number needed to harm.

Results: Cumulative hydrochlorothiazide doses ≥50 000 mg were associated with a significantly increased risk of SCC IRR = 3.05 (1.93–4.81) and BCC IRR = 1.34 (1.06–1.69). Using a 5-year lag-period, hydrochlorothiazide exposure was also associated with a significantly increased risk of lip cancer (IRR 2.85, 95% confidence interval 1.32–6.15). No significantly increased risk of melanoma or oral cavity cancer was observed. Following adjustment for smoking and BMI, which had inverse associations with several skin cancer types, associations for hydrochlorothiazide remained significant. The overall number needed to harm with high-dose cumulative hydrochlorothiazide exposure was: 804 for SCC; 2463 for BCC, and 200 000 for lip cancer but varied by age and sex.

Conclusion: Hydrochlorothiazide exposure was associated with an increased risk of SCC, BCC and lip cancer that is not explained following adjustment for smoking and BMI. These findings may support clinical and regulatory decision making.

KEYWORDS

cancer - oncology, dermatology, medication safety - clinical pharmacology, pharmacoepidemiology - epidemiology

1 | INTRODUCTION

Skin cancers including melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common form of cancer in humans. The incidence of skin cancer varies across the world but has increased over time. In the UK, the age-standardised incidence of melanoma, SCC and BCC are 24, 71 and 151 per 100 000 person years (py) respectively whilst in the USA, the incidence of melanoma and lip cancer are 22.2 and 0.6 per 100 000 py.[1-4] **Hydrochlorothiazide** (HCTZ) is commonly prescribed being used by >10 million patients annually in the USA alone.[5,6] HCTZ is primarily used to manage hypertension but also congestive cardiac failure and oedema. HCTZ can cause photosensitivity and increase UV light-induced DNA damage that could contribute to skin cancer development.[7] In 2013, the International Agency for Research on Cancer classified HCTZ as possibly carcinogenic to humans and called for additional studies to characterise skin cancer risk.[8]

There are limited data examining these risks, particularly among different population types with variable UV skin susceptibility or phenotype.[9] Recently published epidemiological studies from Denmark reported that HCTZ exposure is associated with an increased risk of developing SCC, BCC and lip cancer, whilst associations with melanoma remained less certain.[10-12] However, these studies did not contain data on potentially important confounders of smoking and body mass index (BMI). A safety review of clinical and nonclinical data by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently recommended updating the product information to advise healthcare professionals and patients about the risk of nonmelanoma skin cancers with HCTZ in Europe whilst there are currently no such warnings in the USA. The aim of these studies was to support the PRAC assessment. Their objectives were to evaluate whether similar associations between HCTZ exposure and skin cancer are observed in a different population and data source, to assess the impact of adjusting for smoking and BMI and to estimate absolute risk.

2 | METHODS

2.1 | Data source

The Health Improvement Network (THIN) database contains longitudinal electronic medical records from >600 general practices across the UK. THIN contains data on general practitioners' diagnostics and prescriptions, and lifestyle information. Data are representative of the UK population in terms of age, sex, deprivation status and geographical distribution.[13] Health information are coded using the Read Code clinical classification system, a hierarchical classification system, linked to the International Classification of Diseases.[14] Data quality control measures in THIN include the acceptable mortality reporting date, which is specific to each practice and defines the date from which computerised recording of mortality data reached acceptable standards.[15]

> **What is already known on this subject?**
> - Hydrochlorothiazide can cause skin photosensitivity.
> - Recent observational studies have reported an association between cumulative hydrochlorothiazide exposure and skin cancers.
> - The generalisability of these findings to other populations is uncertain.
>
> **What this study adds**
> - In a UK population high-dose cumulative hydrochlorothiazide exposure was associated with an increased risk of squamous cell carcinoma, basal cell carcinoma and lip cancer.
> - The number needed to harm in one year once high-dose cumulative exposure has occurred was estimated at 804 for squamous cell carcinoma, 2463 for basal cell carcinoma and 200 000 for lip cancer but varied by age and sex.

2.2 | Study design and population

The study used the same designs as the recently published Danish studies,[10-12] with minor deviations representing differences between databases (supplementary Table S1). Cohort entry was defined as the latest of the following criteria: start of the study period (01 January 1999); the practices acceptable mortality reporting date; date of registration with a general practice + 1 year. Cohort exit was defined by the earliest of the following criteria: an outcome event; deregistration from the general practice; death; date of last data collection; end of the study period (01 May 2016). Patients were required to have no previous cancer diagnosis before the index date, i.e. the date of the first skin cancer event occurring after cohort entry for case subjects. For the lip cancer and oral cavity cancer analysis, patients were allowed to have a prior history of nonmelanoma skin cancer (BCC or SCC), in keeping with the Danish study. Patients were required to have no prior record of organ transplantation, human immunodeficiency virus diagnosis or use of immunosuppressant drugs such as **azathioprine**, **cyclosporine** or **mycophenolate mofetil**, at any time before the index date that may predispose to skin cancer risk.

2.3 | Outcomes

Outcomes were defined by Read codes recorded in the patient's electronic medical record (supplementary Table S2). For SCC, we only used Read codes that were described specifically as being skin related. Five outcomes were evaluated: SCC skin cancer; BCC skin cancer; melanoma; lip cancer; and oral cavity cancer. Given that the mechanism of action for this risk is alleged to be photosensitivity, oral cavity cancer was included as a negative control testing for unmeasured

confounding because cancers arising within the oral cavity and pharynx will not be exposed to significant UV-light whilst potentially sharing similar risk factors for cancer development and in particular for lip cancer. Any observed association between HCTZ and oral cavity cancers would raise doubt about the validity of an association between HCTZ and skin cancer due to UV light exposure.

2.4 | Control selection

Controls were randomly selected using incidence density sampling whereby controls are selected from individuals who have not experienced the event at the index date. For the analysis with lip cancer, up to 100 controls were randomly selected matched on sex, exact year of birth and calendar year of cohort entry, applying the same criteria as described for cases. For the remaining outcomes, up to 20 controls were randomly selected matched on sex, exact year of birth and calendar year of cohort entry.

2.5 | Exposure

Ever use of HCTZ was defined as having been issued ≥1 prescription for a HCTZ-containing drug before the index date minus the lag-time period and never use as never having been prescribed a HCTZ-containing prescription before the index date minus the lag-time period. Prescriptions within 2 years of the index date (within the lag-time period) were excluded from the cumulative dose to allow a reasonable induction period on each cancer outcome, with a secondary analysis conducted using a 5-year exposure lag-time period to test the robustness of the results. The dose was identified in all individual eligible prescriptions, and the cumulative dose for each individual prior the index date was calculated. For the lip cancer analysis, high-dose HCTZ use was defined as a cumulative dose ≥25 000 mg, corresponding to 1000 or more defined daily doses (i.e. approximately 3 years of cumulative use). For the remaining outcomes, high-dose HCTZ was defined as a cumulative dose ≥50 000 mg, corresponding to 2000 or more defined daily doses (i.e. approximately 6 years of cumulative use). These were chosen to replicate the recently published Danish studies.[10-12] The list of HCTZ drug codes is contained in Table S3.

2.6 | Confounders

The primary analyses were adjusted for: (i) age and sex (inherent in the matching criteria); any use of the following drugs with suggested photosensitizing properties (retinoids, tetracyclines, macrolides, quinolones, amiodarone); (ii) any use of the following drugs with suggested antineoplastic effects (aspirin, nonsteroidal anti-inflammatory drugs and statins); (iii) history of alcohol abuse, diabetes and chronic obstructive pulmonary disease; (iv) the Charlson comorbidity index score (categorised as 0: low; 1–2: medium; or ≥ 3: high). Exposure to each potential confounder drug was defined as ≥2 prescriptions on separate dates. Covariate information on drugs recorded less than 2 years prior to the index date was disregarded. For model

2, we additionally adjusted for smoking status (nonsmoker, ex-smoker and current smoker) and BMI.

2.7 | Data analysis

Conditional logistic regression was used to calculate odds ratios for the association between each cancer outcome and the cumulative dose categories. Using an incidence density sampling approach, odds ratios calculated in this way represent incidence rate ratios (IRR) that we use to report the effect estimates. Associations are first presented using a 2-year HCTZ exposure lag-time and then using a 5-year HCTZ exposure lag-time. Given the amount of person follow-up in THIN is less than in the Danish registries, associations were evaluated using all patients with sensitivity analysis using patients restricted to those with at least 10 years follow-up. Analyses are first presented matched on exact age and sex only, then adjusted using the approach applied in the Danish studies (adjusted model 1), and by additionally adjusting for smoking status and BMI (adjusted model 2). Multiple imputation was used to impute missing data on smoking and BMI and the imputation model included all variables relating to clinical characteristics, outcome events, medication, and comorbidities. Multiple imputation used fully conditional specification, with linear regression for continuous variables (BMI) and logistic regression for categorical variables (smoking status) with 5 imputations and analysed using Rubin's rules.[16] Adjusted rate differences were calculated for significant associations as described.[17] As the incidence of SCC in the cohort was less than expected, absolute risk estimates for SCC were calculated using published incidence rates rather than the cohort data.[3] In this regard, the adjusted rate difference for SCC was calculated by $(IR \times IRR) - IR$. Rate differences were then used to estimate the number of patients needed to treat to cause 1 additional cancer (number needed to harm) per year overall, and by sex and age category, as reported elsewhere, for high dose cumulative HCTZ exposure.[18,19] Analysis was carried out using SAS Enterprise Guidev7.1 and STATAv15.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, (Harding et al., 2018[20]) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

3 | RESULTS

3.1 | Nested case control populations

Characteristics of cases and controls are presented in Table 1. A total of 7560 incident SCC cases were identified during cohort follow-up (incidence 11.7 per 100 000 py in adults), which were matched to

TABLE 1 Characteristics of matched cases and controls for the full population in the skin, lip and oral cavity cancer case control analyses

	SCC		BCC		Melanoma		Lip cancer		Oral cavity cancer	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Number of individuals	7560	151 194	89 088	1 781 712	11 185	223 700	707	70 500	3516	70 328
Female sex, n (%)	3015 (40.0)	60 300 (40.0)	43 507 (48.8)	870 140 (48.8)	6365 (56.9)	127 300 (56.9)	239 (33.8)	23 700 (33.6)	1175 (33.4)	23 500 (33.4)
Age (y), mean ± SD	74.8 (11.5)	74.8 (11.5)	68.3 (13.6)	68.3 (13.6)	58.2 (16.4)	58.2 (16.4)	63.8 (13.6)	63.8 (13.6)	61.5 (13.2)	61.5 (13.2)
Years of follow-up, mean ± SD*	9.3 (4.4)	9.3 (4.4)	7.2 (4.6)	7.2 (4.6)	7.1 (4.6)	7.1 (4.6)	6.2 (4.2)	6.2 (4.2)	7.3 (4.5)	7.3 (4.5)
Body mass index (kg/m²), mean ± SD	28.0 (5.4)	28.5 (5.5)	27.6 (5.4)	28.1 (5.7)	27.9 (5.8)	28.0 (6.0)	27.1 (6.1)	28.9 (5.7)	27.3 (5.9)	28.3 (5.7)
Missing body mass index, n (%)	636 (8.4)	46 329 (30.6)	10 812 (12.1)	545 587 (30.6)	1581 (14.1)	66 370 (29.7)	136 (19.2)	21 739 (30.8)	527 (15.0)	20 334 (28.9)
Charlson comorbidity index ≥1, n (%)	4133 (54.7)	64 305 (42.5)	37 125 (41.7)	665 808 (37.4)	3466 (31.0)	62 846 (28.1)	316 (44.7)	22 889 (32.5)	1483 (42.2)	21 112 (30.0)
Current smokers, n (%)	910 (12.0)	14 041 (9.3)	9825 (11.0)	205 521 (11.5)	1349 (11.0)	31 614 (11.5)	258 (40.8)	9755 (18.8)	1130 (40.9)	10 355 (19.3)
Missing smoking status, n (%)	180 (2.4)	38 989 (25.7)	6581 (7.4)	468 070 (26.3)	877 (7.8)	55 811 (25.0)	75 (10.6)	18 633 (26.4)	260 (7.4)	19 625 (26.8)
Prior alcohol abuse, n (%)	87 (1.2)	1396 (0.9)	782 (0.9)	17 182 (1.0)	69 (0.6)	2262 (1.0)	62 (8.8)	910 (1.3)	412 (11.7)	966 (1.4)
Retinoid therapy, n (%)	11 (0.2)	92 (0.1)	158 (0.2)	1638 (0.1)	44 (0.4)	456 (0.2)	1 (0.1)	83 (0.1)	6 (0.2)	80 (0.1)
Tetracycline therapy, n (%)	913 (12.1)	11 896 (7.9)	8872 (10.0)	128 530 (7.2)	1019 (9.1)	16 866 (7.5)	56 (7.9)	4453 (6.2)	311 (8.9)	4805 (6.8)
Macrolide therapy, n (%)	1314 (17.4)	17 995 (11.9)	12 012 (13.5)	181 214 (10.2)	1382 (12.4)	23 449 (10.5)	88 (12.5)	6118 (8.7)	424 (12.1)	6838 (9.7)
Amiodarone therapy, n (%)	125 (1.7)	1796 (1.2)	1067 (1.2)	14 505 (0.8)	77 (0.7)	1049 (0.5)	7 (1.0)	478 (0.7)	26 (0.7)	375 (0.5)
Quinolone therapy, n (%)	522 (6.9)	6869 (5.4)	4315 (4.8)	59 731 (3.4)	362 (3.2)	6411 (2.9)	28 (4.0)	1885 (2.7)	130 (3.7)	2054 (2.9)
Aspirin therapy, n (%)	2616 (34.6)	39 420 (26.1)	21 171 (23.8)	327 345 (18.4)	1546 (13.8)	26 265 (11.7)	152 (21.5)	10 819 (15.4)	650 (18.5)	9513 (13.5)
NSAID therapy, n (%)	4003 (53.0)	58 446 (38.7)	39 502 (44.3)	611 882 (34.3)	4002 (35.8)	69 137 (30.9)	277 (39.2)	21 732 (30.8)	1403 (39.2)	22 815 (32.4)
Statin therapy,[a] n (%)	2885 (38.2)	43 374 (28.7)	21 831 (24.5)	337 951 (19.0)	1854 (16.6)	30 861 (13.8)	143 (20.2)	11 611 (16.5)	743 (21.1)	12 098 (17.2)
Hydrochlorothiazide therapy, n (%)	140 (1.9)	1881 (1.2)	958 (1.1)	15 554 (0.9)	86 (0.8)	1407 (0.6)	8 (1.1)	453 (0.6)	26 (0.7)	518 (0.7)
Prior nonmelanoma skin cancer, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	30 (4.2)	1006 (1.4)	1 (0.0)	950 (1.4)

SD = standard deviation; NSAID = nonsteroidal anti-inflammatory drug.

*Years of follow-up = this is the observed mean follow-up measured from cohort entry to the index date.

151 194 controls. The number of cases and controls fell to 4,401 incident SCC cases and 88 449 controls when patients were required to have at least 10 years of follow-up.

A total of 89 088 incident BCC cases were identified during cohort follow-up (incidence 137.5 per 100 000 py in adults), which were matched to 1 781 712 controls. The number of cases and controls fell to 31 253 incident BCC cases and 625 004 controls when patients were required to have at least 10 years of follow-up.

A total of 11 185 incident melanoma skin cancer cases were identified during cohort follow-up (incidence 17.9 per 100 000 py in adults), which were matched to 223 700 controls. The number of cases and controls fell to 3831 incident melanoma cases and 76 656 controls when patients were required to have at least 10 years of follow-up.

A total of 707 incident lip cancer cases were identified during cohort follow-up (incidence 1.1 per 100 000 py in adults), which were matched to 70 500 controls. The number of cases and controls fell to 179 incident lip cancer cases and 18 202 controls when patients were required to have at least 10 years of follow-up.

A total of 3516 incident cases of oral cavity cancer were identified during cohort follow-up (incidence 5.7 per 100 000 py in adults), which were matched to 70 328 controls. The number of cases and controls fell to 1277 incident cases of oral cavity cancer and 25 537 controls when all patients were required to have at least 10 years of follow-up. All patients were well matched on age, sex and follow-up time.

3.2 | Relative risk of skin, lip and oral cavity cancers with hydrochlorothiazide exposure

The relative incidence of SCC was significantly elevated with ever use of HCTZ (IRR =1.22, 95%CI 1.02 to 1.45; Table 2). When stratified by dose, the relative incidence of SCC was significantly elevated with cumulative doses ≥50 000 mg (IRR = 2.93, 95%CI 1.85 to 4.62). Adjustment for smoking status and BMI did not alter the significance of these associations.

The relative incidence of BCC was significantly elevated with ever use of HCTZ (IRR 1.08, 95%CI 1.01 to 1.15; Table 2). When stratified by dose, the relative incidence BCC was elevated with cumulative doses ≥50 000 mg (IRR = 1.30, 95%CI 1.03 to 1.65). When adjusted for smoking status and BMI, cumulative doses ≥50 000 mg remained significantly elevated.

The relative incidence of melanoma was not significantly elevated with ever use of HCTZ (Table 2). When stratified by dose, the relative incidence of melanoma was not significantly elevated with high-dose HCTZ use. Adjustment for smoking status and BMI did not alter the significance of these associations.

The relative incidence of lip cancer was nonstatistically significantly elevated with HCTZ exposure (IRR 1.61, 95%CI 0.71–3.66 and 2.23, 95%CI 0.54–9.16 with 1–24 999 mg and ≥25 000 mg cumulative HCTZ exposure respectively, Table 2). Adjustment for

smoking status and BMI did not alter the significance of these associations. The relative incidence of oral cavity cancer was not significantly elevated with HCTZ exposure (Table 2). Adjustment for smoking status and BMI did not alter the significance of these associations.

3.3 | Secondary analysis

Secondary analyses using the 5-year lag-time are shown in Table 3. Using a 5-year lag-time, the association between HCTZ and lip cancer was significantly elevated (IRR = 2.59, 95%CI 1.20 to 5.60) with 1–24 999 mg cumulative exposure; Table 3). Given the reduced power, it was not possible to estimate the association with cumulative doses ≥25 000 mg using a 5-year lag-time. Other associations examined using a 5-year lag-time were generally in keeping with those using the 2-year lag-time apart from the association with SCC, which was also significantly elevated at lower cumulative doses (≥25 000 mg).

3.4 | Sensitivity analysis

Associations restricting to patients with at least 10 years follow up are presented in Tables S4 and S5. These effect estimates were similar to the primary and secondary analyses but were less precise due to loss of information.

3.5 | Absolute risk of SCC, BCC and lip cancer with hydrochlorothiazide exposure

Adjusted rate differences per 100 000 patients for incident SCC, BCC and lip cancer are presented in Table 4. Cumulative exposure to ≥50 000 mg of HCTZ was estimated to cause 124 additional cases of SCC per 100 000 py, 40 additional cases of BCC per 100 000 py and 1 additional case of lip cancer per 200 000 py. The absolute risk was greater in people aged 60 years and over (383 additional cases of SCC per 100 000 py, 162 additional cases of BCC per 100 000 py and > 5 additional cases of lip cancer per 200 000 py). Depending on the category evaluated, the number needed to harm per year ranged from: 261 to 4167 for SCC; 618 to 3610 for BCC; and 37 037 to 500 000 for lip cancer.

3.6 | Association of skin, lip and oral cavity cancer with smoking and BMI

The associations between the different cancers and smoking and BMI are shown in Table 5. Smoking was associated with a significantly increased risk of lip and oral cavity cancers. In contrast smoking was inversely associated with BCC and melanoma risk. There were no strong associations with smoking and SCC. A BMI of ≥30 kg/m^2 was

TABLE 2 Association between hydrochlorothiazide exposure and skin, lip and oral cavity cancer using a 2 year lag-time

All patients	Cases	Controls	Crude IRR[a]	Adjusted IRR[b]	Adjusted IRR with smoking & BMI[c]
Squamous cell carcinoma					
Nonuse	7420	149 313	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	140	1881	1.50 (1.26–1.78)	1.22 (1.02–1.45)	1.25 (1.05–1.48)
Cumulative amount (mg)					
▪ 1–24 999	89	1403	1.28 (1.03–1.59)	1.03 (0.83–1.28)	1.05 (0.84–1.30)
▪ 25 000–49 999	29	347	1.69 (1.15–2.47)	1.38 (0.95–2.03)	1.44 (0.98–2.11)
▪ ≥50 000	22	131	3.40 (2.16–5.35)	2.93 (1.85–4.62)	3.05 (1.93–4.81)
Basal cell carcinoma					
Nonuse	88 130	1 766 158	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	958	15 554	1.24 (1.16–1.32)	1.08 (1.01–1.15)	1.10 (1.03–1.17)
Cumulative amount (mg)					
▪ 1–24 999	714	11 756	1.13 (1.04–1.24)	1.06 (0.98–1.14)	1.08 (0.995–1.16)
▪ 25 000–49 999	169	2758	1.21 (1.03–1.43)	1.08 (0.92–1.26)	1.10 (0.94–1.29)
▪ ≥50 000	75	1040	1.42 (1.10–1.84)	1.30 (1.03–1.65)	1.34 (1.06–1.69)
Melanoma					
Nonuse	11 099	222 293	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	86	1407	1.23 (0.99–1.53)	1.11 (0.89–1.38)	1.09 (0.88–1.36)
Cumulative amount (mg)					
▪ 1–24 999	66	1081	1.23 (0.95–1.57)	1.11 (0.86–1.42)	1.08 (0.85–1.40)
▪ 25 000–49 999	16	246	1.31 (0.79–2.17)	1.18 (0.71–1.96)	1.17 (0.70–1.94)
▪ ≥50 000	4	80	1.00 (0.37–2.74)	0.90 (0.33–2.45)	0.89 (0.33–2.43)
Lip cancer					
Nonuse	699	70 047	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	8	453	1.78 (0.88–3.61)	1.63 (0.80–3.33)	1.77 (0.88–3.61)
Cumulative amount (mg)					
▪ 1–24 999	6	345	1.75 (0.78–3.95)	1.61 (0.71–3.66)	1.82 (0.80–4.14)
▪ 25 000–49 999	2	108	2.35 (0.58–9.59)	2.23 (0.54–9.16)	2.12 (0.52–8.74)
▪ ≥50 000	0	22	-	-	-
Oral cavity cancer					
Nonuse	3490	69 802	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	26	518	1.00 (0.68–1.49)	0.84 (0.56–1.26)	0.90 (0.60–1.36)
Cumulative amount (mg)					
▪ 1–24 999	22	387	1.14 (0.74–1.75)	0.94 (0.60–1.46)	1.01 (0.64–1.57)
▪ 25 000–49 999	3	104	0.58 (0.18–1.82)	0.51 (0.16–1.61)	0.53 (0.17–1.69)
▪ ≥50 000	1	27	0.74 (0.10–5.46)	0.74 (0.10–5.50)	0.88 (0.12–6.58)

[a]Matched on sex and age only. [b]Additionally adjusted for; any use of selected drugs with suggested photosensitizing properties (retinoids, tetracyclines, macrolides, quinolones, amiodarone); any use of drugs with suggested antineoplastic effects (aspirin, nonsteroidal anti-inflammatory drugs, and statins); history of alcohol abuse, diabetes and chronic obstructive pulmonary disease; the Charlson comorbidity index. [c]Adjusted for confounders in B plus smoking status and BMI.

associated with a significantly reduced risk of SCC, BCC, melanoma and oral cavity cancer.

4 | DISCUSSION

We found that HCTZ exposure was associated with a significantly increased relative incidence of SCC, BCC and lip cancer that varied according to cumulative HCTZ dose and definition of the exposure

lag-time period used. However, whilst no significantly increased risk was observed with melanoma, a small increase cannot be excluded based on the available data.

The main studies investigating HCTZ and skin cancer were conducted in Denmark were cumulative HCTZ exposure of ≥50 000 mg was associated with a 1.3-fold increased risk of BCC and a 4-fold increased risk of SCC.[10] Our study demonstrated similar sized effect estimates for BCC and SCC associated with ≥50 000 mg of

TABLE 3 Association between hydrochlorothiazide exposure and skin, lip and oral cavity cancer using a 5 year lag-time

All patients	Cases	Controls	Adjusted IRR[a]	Adjusted IRR[b]	Adjusted IRR with smoking and BMI[c]
Squamous cell carcinoma					
Nonuse	7458	149 791	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	102	1403	1.46 (1.19–1.79)	1.19 (0.97–1.46)	1.22 (0.99–1.50)
Cumulative amount (mg)					
▪ 1–24 999	68	1131	1.21 (0.95–1.55)	0.98 (0.76–1.25)	0.99 (0.77–1.27)
▪ 25 000–49 999	23	204	2.27 (1.48–3.50)	1.90 (1.23–2.94)	2.00 (1.30–3.09)
▪ ≥50 000	11	68	3.27 (1.73–6.20)	2.77 (1.46–5.29)	2.91 (1.53–5.55)
Basal cell carcinoma					
Nonuse	88 437	1 770 860	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	651	10 852	1.20 (1.11–1.30)	1.04 (0.96–1.13)	1.06 (0.98–1.15)
Cumulative amount (mg)					
▪ 1–24 999	523	8708	1.20 (1.10–1.32)	1.04 (0.95–1.13)	1.06 (0.97–1.16)
▪ 25 000–49 999	82	1547	1.06 (0.85–1.33)	0.93 (0.74–1.16)	0.95 (0.76–1.18)
▪ ≥50 000	46	597	1.55 (1.14–2.09)	1.41 (1.04–1.90)	1.44 (1.07–1.95)
Melanoma					
Nonuse	11 123	222 759	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	62	941	1.32 (1.02–1.71)	1.19 (0.92–1.54)	1.18 (0.91–1.53)
Cumulative amount (mg)					
▪ 1–24 999	50	768	1.31 (0.98–1.74)	1.18 (0.88–1.57)	1.16 (0.87–1.55)
▪ 25 000–49 999	11	127	1.74 (0.94–3.23)	1.58 (0.85–2.93)	1.57 (0.85–2.92)
▪ nu 50 000	1	46	0.44 (0.06–3.16)	0.38 (0.05–2.75)	0.37 (0.05–2.69)
Lip cancer					
Nonuse	700	70 214	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	7	286	2.48 (1.16–5.29)	2.15 (1.00–4.63)	2.31 (1.07–4.97)
Cumulative amount (mg)					
▪ 1–24 999	7	240	2.96 (1.38–6.32)	2.59 (1.20–5.60)	2.85 (1.32–6.15)
▪ ≥25 000	0	46	-	-	-
Oral cavity cancer					
Nonuse	3497	69 968	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ever use	19	360	1.06 (0.67–1.68)	0.89 (0.56–1.44)	0.96 (0.60–1.55)
Cumulative amount (mg)					
▪ 1–24 999	17	298	1.14 (0.70–1.87)	0.95 (0.57–1.56)	1.00 (0.60–1.67)
▪ ≥25 000	2	62	0.65 (0.16–2.65)	0.62 (0.15–2.56)	0.73 (0.18–3.01)

[a]Matched on sex and age only. [b]Additionally adjusted for; any use of selected drugs with suggested photosensitizing properties (retinoids, tetracyclines, macrolides, quinolones, amiodarone); any use of drugs with suggested antineoplastic effects (aspirin, nonsteroidal anti-inflammatory drugs and statins); history of alcohol abuse, diabetes and chronic obstructive pulmonary disease; the Charlson comorbidity index. [c]Adjusted for confounders in B plus smoking status and BMI.

cumulative HCTZ exposure. Although Pottegård et al. reported a significant 1.2-fold increased risk with ≥50 000 mg of cumulative exposure and malignant melanoma, no dose–response relationship was observed and the clinical implication of the results are less uncertain.[12] We found no significant association between HCTZ exposure and melanoma although we were not able to evaluate the association between melanoma and ≥50 000 mg cumulative HCTZ dose adequately due to estimates being less precise. Two earlier Danish studies assessing melanoma risk with HCTZ reported contrasting results with

1 reporting a 1.4-fold significantly increased risk of melanoma whilst the other found no significant association.[21,22]

One recent Danish study reported a 2-fold increased risk of lip cancer with ever use of HCTZ, and a 4-fold increase with ≥25 000 mg of cumulative exposure[11] We observed similar sized effect estimates in the primary analysis although they were not statistically significant. However, when the lag-time prior to the index date was increased the observed associations between lip cancer and HCTZ exposure were strengthened, as occurred in the Danish study, and became

TABLE 4 Absolute risk of squamous cell carcinoma, basal cell carcinoma and lip cancer with high dose cumulative hydrochlorothiazide exposure overall and stratified by age and sex categories

Cancer type	Adjusted rate difference per 100 000 person years	Number needed to harm per year
SCC with ≥50 000 mg cumulative dose		
▪ overall	124.4 (56.5–231.3)	804
▪ male	219.8 (99.7–408.4)	455
▪ female	71.3 (32.4–132.6)	1402
▪ aged 40–59 y	24.0 (10.9–44.6)	4167
▪ aged 60 y and over	383.4 (173.9–712.5)	261
BCC with ≥50 000 mg cumulative dose		
▪ overall	40.6 (32.2–51.3)	2463
▪ male	52.4 (41.4–66.1)	1909
▪ female	31.1 (24.6–39.2)	3216
▪ aged 40–59 y	27.7 (21.9–34.9)	3610
▪ aged 60 y and over	161.9 (128.1–204.2)	618
Lip cancer with 1–24 999 mg cumulative dose*		
▪ overall	0.5 (0.3–1.2)	20 0000
▪ male	0.8 (0.4–1.7)	125 000
▪ female	0.4 (0.2–0.9)	250 000
▪ aged 40–59 y	0.2 (0.1–0.4)	500 000
▪ aged 60 y and over	2.7 (1.2–5.8)	37 037

SCC = squamous cell carcinoma skin cancer; BCC = basal cell carcinoma skin cancer.

*Lip cancer adjusted rate difference = calculated with significant model 2 estimates using a 5-year lag-time.

BCC adjusted rate difference = calculated with significant model 2 estimates using a 2-year lag-time.

SCC adjusted rate difference = calculated using the IRR and published UK incidence rates for SCC.[3]

significant. The lag-time period is the period in which any exposure is assumed to mechanistically be noncausal due to the potential latency required for skin cancer development. Therefore, during such a lag-time period any prescriptions for HCTZ are disregarded.

We evaluated oral cavity cancer as a negative control to test the potential mechanism that photosensitivity specifically increases the risk of skin cancers. We consistently found no elevated association between HCTZ exposure and incident oral cavity cancer development, suggesting that unmeasured confounding by risk factors common to skin/lip cancer and oral cavity cancer does not explain the observed associations.

4.1 | Strengths and weaknesses of the study

Although our analyses attempted to replicate the Danish studies in another European data source and population, the available power for analysis and subtle differences between databases, covariates and method of diagnosis may have influenced the strength of observed associations. The THIN database is a large data source but it does not have the same national coverage or longitudinal follow-up as do registries in Denmark. This meant that more in-depth exploration of the association between HCTZ exposure and skin cancer outcome could not be provided using the current data. Despite these differences, we observed similar associations that do not appear to be explained by common sources of heterogeneity including from differences in healthcare delivery or data recording. We also adjusted for missing potential confounders of smoking and BMI. Although these are perhaps stronger confounders for the lip and oral cavity cancer outcomes it has recently been reported that smoking is inversely associated with melanoma development, an effect that we also observed in our study.[23,24]

BMI was evaluated because it has been shown to influence a wide range of cancer development or progression including melanoma.[25,26] We observed other significant inverse associations with BMI of 30 or greater for all cancers apart from lip cancer, the reasons for which are uncertain. Whilst adjustment for these may have only

TABLE 5 Associations between different skin, lip and oral cavity cancer and smoking and BMI

	SCC IRR	BCC IRR	Melanoma IRR	Lip cancer IRR	Oral cavity cancer IRR
Smoking					
Nonsmoker	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Ex-smoker	0.91 (0.86–0.97)	0.97 (0.95–0.99)	0.93 (0.89–0.97)	1.37 (1.08–1.74)	1.15 (1.04–1.27)
Current smoker	0.98 (0.90–1.06)	0.75 (0.72–0.75)	0.65 (0.61–0.69)	3.48 (2.75–4.42)	2.63 (2.34–2.96)
Body mass index (kg/m^2)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25–29.9	1.01 (0.95–1.07)	0.94 (0.92–0.96)	1.04 (0.99–1.09)	0.96 (0.78–1.18)	0.81 (0.73–0.89)
≥30	0.79 (0.74–0.84)	0.75 (0.73–0.76)	0.92 (0.87–0.98)	1.10 (0.88–1.38)	0.73 (0.65–0.82)

IRR = incidence rate ratios following adjusted for all confounders in contained in model 2.

slightly influenced the size of the effect estimates for HCTZ it had negligible impact on their statistical significance suggesting that, in this instance at least, missing data on these characteristics may not be critical for similar studies examining HCTZ exposure where information on smoking or BMI is not available. Other unmeasured confounding remains possible such as surveillance bias though we observed no association with oral cavity cancer, which should be subject to similar issues. This provides stronger evidence that the observed associations may be causal and related to photosensitivity. Only relatively few oral cavity cancer cases were detected compared to BCC, SCC or melanoma, meaning that associations between oral cavity cancer and HCTZ may be less precise. However, the observed associations with HCTZ were either close to the null or inversely associated with oral cavity cancer, unlike with skin cancer, suggesting that it is less likely that we are missing a significant association because of insufficient power. The recent Danish studies used pathologically validated outcomes whilst THIN outcomes used primary care diagnostic coding only. However, the incidence of each skin cancer in our studies was similar to UK national cancer registrations, apart from SCC, where incidence in primary care records was lower. This probably relates to the use of Read codes that only specified squamous carcinoma as being skin related in an attempt to improve validity. This will underestimate the absolute risk for SCC if it is calculated using our cohort data, which is the reason we used published incidence rates for SCC from the UK instead.[3]

4.2 | Implications for practice

In 2018, PRAC considered that it was biologically plausible that nonmelanoma skin cancer may occur following higher cumulative doses of HCTZ, which resulted in special precautions being added to the product information. This stated that patients taking HCTZ should be informed of the risk of nonmelanoma skin cancer and advised to check their skin and report suspicious lesions.[27] Possible preventive measures are also suggested such as limited exposure to sunlight and, in case of exposure, adequate skin protection. This information was communicated via a direct healthcare professional communication, a common method of communicating safety warnings that may be associated with greater impact compared to other communication methods such as drug bulletins.[28,29] Our studies were undertaken to support the EMA PRAC assessment and provide further evidence suggesting a causal association between exposure to HCTZ and nonmelanoma and lip cancers related to photosensitivity. The frequency of these skin cancers in the HCTZ summary of product characteristics in Europe is listed as not known. We estimated the number of additional cancers that may arise per year following cumulative HCTZ exposure after the procedure was closed. For all cancer types, it is notable that absolute risk from cumulative HCTZ exposure is much greater in those aged over 60 years. There was some evidence that absolute risk was also greater in men. This information may potentially support an update to the product information regarding the frequency of such events. Further studies examining the risk of skin cancer with

HCTZ in different UV-susceptible skin susceptible populations are required to assess whether these effects are more generalizable, similar to the recently published study using data from Taiwan.[30]

5 | CONCLUSIONS

In a UK population, evidence suggests that exposure to HCTZ was associated with an increased risk of incident nonmelanoma skin and lip cancers. This information may be useful to healthcare professionals for assessing the benefit–risk and communicating the risk of these medicines to patients.

COMPETING INTERESTS
The authors (D.M., J.S., A.P., X.K.) have no conflicts of interest in connection with this article. D.M. is a member of the EMA Pharmacovigilance Risk Assessment Committee.

CONTRIBUTORS
All authors were involved in the study design. D.M. collected the data, performed the analysis and is the guarantor for the study. All authors contributed to the interpretation of results, writing the manuscript and approved the final draft. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA AVAILABILITY STATEMENT
No data are available for sharing. Data can be accessed according to IQVIA's standard terms and conditions for using the THIN database.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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