Hydrochlorothiazide use and risk for Merkel cell carcinoma and malignant adnexal skin tumors: A nationwide case-control study

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Background: Hydrochlorothiazide use has been associated with markedly increased risk for squamous cell carcinoma. No previous studies have investigated the association between hydrochlorothiazide use and the risk for Merkel cell carcinoma (MCC) and malignant adnexal skin tumors (MAST).

Objective: To examine the association between hydrochlorothiazide use and the risk for MCC and MAST.

Methods: Using Danish nationwide health registries, we identified all patients with incident MCC or MAST during 2004-2015 and matched the cases individually to cancer-free population controls by risk set sampling. Using conditional logistic regression, we estimated the odds ratios (ORs) and confidence intervals (CIs) associated with cumulative use of hydrochlorothiazide.

Results: The adjusted ORs for MCC and MAST associated with high use (≥50,000 mg) of hydrochlorothiazide was 2.3 (95% CI 1.1-4.8) and 3.6 (95% CI 1.9-7.0), respectively, which increased to 3.3 (95% CI 1.3-8.3) and 5.6 (95% CI 2.4-13.3), respectively, with highest use (≥100,000 mg). We found no increased risk for these tumors in analyses of drugs with similar indications as hydrochlorothiazide, except there was a tendency toward an increased risk for MCC associated with the use of furosemide (OR 1.9, 95% CI 0.9-4.0).

Limitations: No data on sun exposure was available.

Conclusion: Hydrochlorothiazide use is associated with an increased risk for MCC and MAST. (J Am Acad Dermatol 2019;80:460-5.)

Key words: antihypertensives; epidemiology; hydrochlorothiazide; malignant adnexal skin tumors; Merkel cell carcinoma; pharmacology; skin cancer.

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Hydrochlorothiazide is a widely used diuretic and antihypertensive drug[1,2] known to possess photosensitizing properties.[3] Recent studies have associated hydrochlorothiazide use with increased risks for lip cancer, nonmelanoma skin cancer (basal cell carcinoma and squamous cell carcinoma), and melanoma.[4-6]

Considering the shared risk factor of ultraviolet (UV) radiation, drug photosensitivity could also be implicated in the development of other rarer types of nonmelanoma skin cancer, eg, Merkel cell carcinoma and malignant adnexal skin tumors.[7-9] Merkel cell carcinoma is a rare neuroendocrine tumor of the skin, believed to develop from Merkel cells, which are mechanoreceptors of the skin.[7] Malignant adnexal skin tumors are a heterogeneous group of neoplasms deriving from adnexal structures in the skin, including eccrine or apocrine sweat glands, hair follicles, and sebaceous glands.[9] Risk factors for Merkel cell carcinoma include increased age, light skin type, UV radiation, and immunosuppression. A polyomavirus has been found in the genome of 80% of Merkel cell carcinomas.[10] Although the etiology of malignant adnexal skin tumors is less elucidated, similar risk factors have been suggested (except for emergence of polyomavirus), including UV radiation.[11-14]

Despite the involvement of UV radiation in the etiology and pathogenesis of Merkel cell carcinoma and malignant adnexal skin tumors, only a few previous studies have examined the effect of photosensitizing drug use on the risk for these tumors. To our knowledge, only 1 study has examined the association between use of diuretics and risk for Merkel cell carcinoma[15]; however, hydrochlorothiazide use was not specifically addressed.

These considerations inspired us to conduct a nationwide study on the association between use of hydrochlorothiazide and risk for Merkel cell carcinoma and malignant adnexal skin tumors.

CAPSULE SUMMARY

- Hydrochlorothiazide has photosensitizing properties and has been linked to nonmelanoma skin cancer.
- We found evidence of a positive dose-response relationship for cumulative use of hydrochlorothiazide and risk for Merkel cell carcinoma and malignant adnexal skin tumors.
- Use of hydrochlorothiazide should be carefully considered in patients at high risk for skin cancer.

METHODS

We performed a nested case-control study, similarly to our recent studies,[4-6] on the basis of the nationwide Danish demographic and health registries (Supplementary Appendix; available at http://www.jaad.org).

From the Danish Cancer Registry,[16] we identified patients (cases) with a histologically verified primary diagnosis of Merkel cell carcinoma or malignant adnexal skin tumor during January 1, 2004-December 31, 2015 (study period). Supplemental Table I (available at http://www.jaad.org) provides definitions of all study variables, including codes for Merkel cell carcinoma and malignant adnexal skin tumor. The date of diagnosis recorded in the Danish Cancer Registry was defined as the index date. We required that patients had resided in Denmark for at least 10 consecutive years before the index date; have no previous records of cancer, organ transplantation, or HIV infection; and have no recorded use of azathioprine, cyclosporine, or mofetil mycophenolate.

For each case, we used risk set sampling and randomly matched 20 population controls by sex and birth year, applying the same eligibility criteria as was done for cases. Controls were allotted the same index date as their corresponding cases.

We retrieved prescription data from 1995 up to 2 years before the index date for both cases and controls. Hydrochlorothiazide ever use was defined as having redeemed at least 1 prescription of a hydrochlorothiazide-containing drug during this period and never use as having no prescription record of a hydrochlorothiazide-containing preparation. The content of hydrochlorothiazide was determined in all combination or single drugs dispensed to the study patients. On the basis of this information, we could estimate each person's cumulative use of hydrochlorothiazide.

Main analyses

We used conditional logistic regression to calculate minimal (age and sex by design) and multivariable odds ratios (ORs) and 95% confidence intervals (CIs) comparing high use of hydrochlorothiazide (≥50,000 mg) among patients with Merkel cell carcinoma or malignant adnexal skin tumor with use among cancer-free controls. The multivariable models additionally included the following predefined potential confounders or risk factors: a) use of

Abbreviations used:

CI: confidence interval
OR: odds ratio
UV: ultraviolet

topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, methoxypsoralene, and amiodarone; b) use of aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, steroids, or statins; c) history of conditions indicative of heavy alcohol consumption, diabetes, chronic renal insufficiency, or chronic obstructive pulmonary disease; d) Charlson Comorbidity Index score (0 low, 2 medium, or ≥3 high); and e) highest achieved education (short, medium, long, or unknown).

To examine potential dose-response relationships, we also examined ORs according to predefined categories of cumulative hydrochlorothiazide use. We repeated main analyses for other diuretics and antihypertensives and other drugs with suggested photosensitizing properties.

We considered Merkel cell carcinoma and malignant adnexal skin tumors separately in all analyses. Never use of hydrochlorothiazide constituted the reference group.

Supplementary and sensitivity analyses

First, we repeated the main analyses for drugs with comparable indications to hydrochlorothiazide and suggested photosensitizing properties: bendroflumethiazide (the thiazide most commonly used in Denmark) and furosemide (loop diuretic).[17-19] Next, we performed analyses for other antihypertensives with indications comparable to thiazides (ie, primarily mild-to-moderate hypertension), including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and group 2 calcium channel blockers. In the analyses of other diuretics and nondiuretic antihypertensives, we adjusted ORs for hydrochlorothiazide use. We also performed subgroup analyses according to age and sex or with restriction to specific subsets of the study population: never users of other photosensitizing drugs (defined previously); those with low comorbidities (Charlson Comorbidity Index score 0); persons with no history of diabetes or chronic renal insufficiency, as patients with diabetes or renal insufficiency are known to have an overall increased risk for cancer; persons with no history of actinic keratosis, which is associated with exposure to UV light and considered a precursor of nonmelanoma skin cancer; and persons with no history of atopic dermatitis or psoriasis, which is associated with exposure to UV light and possibly associated with nonmelanoma skin cancer risk.[20,21] Last, we repeated the main analyses, varying the lag time from 0 to 5 years (in steps of 6 months).

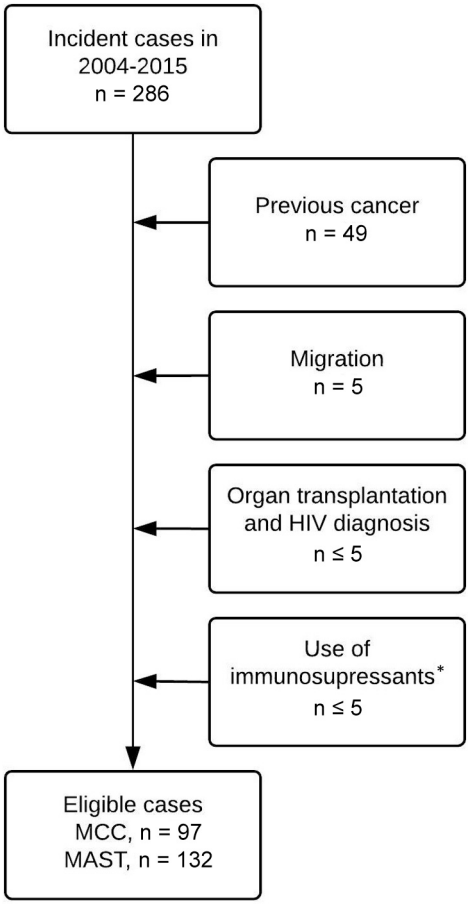

Fig 1. Flowchart of case selection. *Azathioprine, cyclosporine, and mycophenolate mofetil. *MAST*, Malignant adnexal skin tumor; *MCC*, Merkel cell carcinoma.

Ethical approval and statistical analysis

The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study. According to Danish law, ethics approval is not required for registry-based studies. All analyses were performed using STATA release 14.1 (StataCorp, College Station, TX).

RESULTS

We included 97 patients with Merkel cell carcinoma and 132 with malignant adnexal skin tumors (Fig 1) matched to 1857 and 2620 population controls, respectively. Baseline characteristics were similar between patients with malignant adnexal skin tumors and controls (Table I); however, Merkel cell carcinoma patients had higher numbers of comorbidities and drug use, in particular of the

Table I. Characteristics of patients with Merkel cell carcinoma or malignant adnexal skin tumor cases and their matched controls

	Merkel cell carcinoma		Malignant adnexal skin tumor	
Characteristic	**Cases, N = 97**	**Controls, N = 1857**	**Cases, N = 132**	**Controls, N = 2620**
Age, years, median (IQR)	80 (70-87)	79 (70-86)	73 (61-79)	73 (61-79)
Male sex	38 (39.2)	760 (40.9)	63 (47.7)	1240 (47.3)
Use of photosensitizing drugs				
Topical retinoids	–	n < 5	–	5 (0.2)
Oral retinoids	n < 5	7 (0.4)	n < 5	11 (0.4)
Tetracycline	n < 5	32 (1.7)	n < 5	42 (1.6)
Macrolides	35 (36.1)	414 (22.3)	27 (20.5)	584 (22.3)
Aminoquinoline	20 (20.6)	115 (6.2)	n < 5	156 (6.0)
Amiodarone	n < 5	17 (0.9)	n < 5	12 (0.5)
Methoxypsoralene	–	n < 5	–	n < 5
Other drug use				
Aspirin	44 (45.4)	634 (34.1)	36 (27.3)	693 (26.5)
Non-aspirin NSAID	66 (68.0)	1064 (57.3)	81 (61.4)	1399 (53.4)
Statins	34 (35.1)	462 (24.9)	32 (24.2)	568 (21.7)
Steroids	35 (36.1)	314 (16.9)	20 (15.2)	362 (13.8)
Diagnoses				
Alcohol-associated conditions	n < 5	36 (1.9)	5 (3.8)	79 (3.0)
Diabetes	19 (19.6)	187 (10.1)	11 (8.3)	247 (9.4)
COPD	10 (10.3)	144 (7.8)	6 (4.5)	184 (7.0)
Chronic renal insufficiency	n < 5	28 (1.5)	n < 5	36 (1.4)
CCI score				
0	43 (44.3)	1132 (61.0)	87 (65.9)	1707 (65.2)
1	26 (26.8)	415 (22.3)	19 (14.4)	535 (20.4)
2	9 (9.3)	171 (9.2)	16 (12.1)	204 (7.8)
≥3	19 (19.6)	139 (7.5)	10 (7.6)	174 (6.6)
Education				
Short, 7-10 years	33 (34.0)	737 (39.7)	48 (36.4)	1044 (39.8)
Medium, 11-12 years	34 (35.1)	495 (26.7)	52 (39.4)	877 (33.5)
Long, ≥13 years	9 (9.3)	288 (15.5)	22 (16.7)	510 (19.5)
Unknown	21 (21.6)	337 (18.1)	10 (7.6)	189 (7.2)

Data are presented as n (%) unless otherwise noted.
CCI, Charlson Comorbidity Index; *COPD*, chronic obstructive pulmonary disease; *HCTZ*, hydrochlorothiazide; *IQR*, interquartile range; *NSAID*, nonsteroidal anti-inflammatory drug.

photosensitizing drugs macrolides and aminoquinolines, and had a higher level of education compared with their controls.

We observed high use of hydrochlorothiazide among Merkel cell carcinoma patients (11.3%) than controls (4.7%), yielding an OR of 2.3 (95% CI 1.1-4.8). The corresponding figures for patients with malignant adnexal skin tumors and controls were 9.8% and 2.8%, respectively, equivalent to an OR of 3.6 (95% CI 1.9-7.0) (Table II).

We found evidence of a positive dose-response relationship with cumulative hydrochlorothiazide use for both Merkel cell carcinoma and malignant adnexal skin tumors, with ORs increasing to 3.3 (95% CI 1.3-8.3, test for trend $P < .01$) for Merkel cell carcinoma and 5.6 (95% CI 2.4-13.3, test for trend $P < .01$) for malignant adnexal skin tumors in the highest exposure category (≥100,000 mg) (Table II).

Restricting analyses to individuals with no recorded use of photosensitizing drugs other than hydrochlorothiazide had little effect on the associations (Merkel cell OR 2.1, 95% CI 0.7-6.2; malignant adnexal skin tumors OR 2.4, 95% CI 0.9-6.1). We found no increase in risk for Merkel cell carcinoma or malignant adnexal skin tumors in analyses of drugs with similar indications as hydrochlorothiazide (Supplemental Tables II–VI; available at http://www.jaad.org), except a tendency toward an increased risk of Merkel cell carcinoma associated with the use of furosemide (OR 1.9, 95% CI 0.9-4.0, Supplemental Table III). Last, we observed increasing ORs with increasing lag time for

Table II. Association between exposure to hydrochlorothiazide and risk for Merkel cell carcinoma or malignant adnexal skin tumor

Subgroup	Cases, N = 97	Controls, N = 1857	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Merkel cell carcinoma				
Nonuse	77	1549	1.0 (referent)	1.0 (referent)
Ever use	20	308	1.4 (0.8-2.3)	1.0 (0.6-1.8)
High use ≥50,000 mg	11	87	2.7 (1.3-5.3)	2.3 (1.1-4.8)
Cumulative amount, mg				
1-49,999	9	221	0.9 (0.4-1.8)	0.6 (0.3-1.3)
50,000-99,999	n < 5	45	—	—
≥100,000	7	42	3.7 (1.6-8.7)	3.3 (1.3-8.3)
Malignant adnexal skin tumor	N = 132	N = 2620		
Nonuse	111	2311	1.0 (referent)	1.0 (referent)
Ever use	21	309	1.4 (0.9-2.4)	1.4 (0.9-2.4)
High use	13	73	3.7 (1.9-7.0)	3.6 (1.9-7.0)
Cumulative amount, mg				
1-49,999	8	236	0.7 (0.4-1.6)	0.7 (0.4-1.6)
50,000-99,999	5	46	2.3 (0.9-6.1)	2.4 (0.9-6.5)
≥100,000	8	27	5.8 (2.5-13.3)	5.6 (2.4-13.3)

CI, Confidence interval; *OR*, odds ratio.

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

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

hydrochlorothiazide use (Supplemental Table VII; available at http://www.jaad.org).

DISCUSSION

In this large nationwide population-based study, we found a 2.3-fold increased risk for Merkel cell carcinoma and a 3.6-fold increased risk for malignant adnexal skin tumors associated with high use of hydrochlorothiazide.

Epidemiologic studies of risk factors of these rare skin tumors are scarce. The use of nationwide Danish registries enabled the identification of cases and controls with low risk for selection bias. Case diagnoses were histologically verified, further enhancing validity. We had detailed and continuously updated prescription data up to a maximum of 18 years to assess drug use among patients and controls and detailed information on comorbidities, concomitant drug use, and sociodemographic characteristics. Study limitations were primarily the lack of information on the major risk factors UV-light exposure, skin phenotype, and (for Merkel cell carcinoma cases) infection with polyomavirus. Nevertheless, we find it unlikely that prevalence of these risk factors would differ substantially between users and nonusers of hydrochlorothiazide to a degree that it could explain our results.

Evidence is sparse on photosensitizing drugs and risk for Merkel cell carcinoma or malignant adnexal skin tumors. In a previous Danish study, Kaae et al[15] investigated the association between photosensitizing diuretics and risk for Merkel cell carcinoma, but they did not include hydrochlorothiazide in their analyses. Noteworthy, similar to the finding in our study, Kaae et al also observed a moderately increased risk for Merkel cell carcinoma associated with furosemide use (incidence rate ratio 1.6).

Hydrochlorothiazide is classified as a possible carcinogenic drug by the International Agency of Research on Cancer.[22] The hypothesis is that long-term exposure to hydrochlorothiazide has detrimental effects on the repair mechanisms of skin cells. As increased UV-light exposure increases DNA damage to skin cells, concurrent long-term exposure to hydrochlorothiazide leads to increased likelihood of skin malignancy, including Merkel cell carcinoma and malignant adnexal skin tumors. The dose-response patterns and the neutral results in analyses of drugs with similar indications as hydrochlorothiazide, observed for both Merkel cell carcinoma and malignant adnexal skin tumors further substantiate the association of these rare tumors with use of hydrochlorothiazide. In conjunction with our previous reports on nonmelanoma and melanoma skin cancer risk,[4-6] the present findings indicate that use of hydrochlorothiazide is associated with increased risk for all types of UV-light–associated skin cancers. If this indeed is the case, UV-light exposure can be

considered an effect modifier of the association between hydrochlorothiazide use and the cancers we studied (ie, Merkel cell carcinoma and malignant adnexal skin tumors). We could not perform analyses to substantiate this claim as our data contained no information on UV-light exposure.

Merkel cell carcinoma is an aggressive cancer with a high risk for local, regional, and distant recurrence. A large study of Merkel cell carcinoma in the United States reported a 5-year overall survival of only 40%.[23] A larger variation in prognosis is seen for the heterogeneous group of malignant adnexal skin tumors, with most tumors being only locally aggressive; however, metastasizing has been reported in 12% of patients, with an overall 5-year survival of 73%.[9] Therefore, it is of significant clinical relevance to identify potentially modifiable risk factors for both Merkel cell carcinoma and malignant adnexal skin tumor. Our results suggest that avoidance of hydrochlorothiazide use might affect survival rates. In conclusion, our study indicates that use of hydrochlorothiazide increases the risk for Merkel cell carcinoma and malignant adnexal skin tumor.

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SUPPLEMENTARY APPENDIX. DANISH NATIONWIDE HEALTH REGISTRIES

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and provides accurate and almost complete records of cancer cases in Denmark. Cancer diagnoses are coded according to the International Classification of Diseases, Tenth Revision (ICD-10); and the ICD for oncology (ICD-O-1-3) indicates topography and morphology.

The Danish National Prescription Registry contains data on all prescription drugs filled by Danish residents since 1995. The data include the type of drug, date of filling, and quantity. The dosing information and the indication for prescribing are not available, and no information is available on the drugs used at the hospital level. Drugs are categorized according to the Anatomic Therapeutic Chemical Index, a hierarchical classification system developed by the World Health Organization, and the quantity dispensed for each prescription is described by the number and strength of the pharmaceutical entities (eg, tablets), as well as defined daily doses.

The Danish National Registry of Patients contains nationwide data on all nonpsychiatric hospital admissions since 1977 and on ambulatory hospital contacts and psychiatric admissions since 1995. Discharge and contact diagnoses have been coded according to ICD-8 from 1977 to 1993 and ICD-10 since 1994.

Statistics Denmark, is a governmental institution that collects and processes information for a variety of statistical and scientific purposes, eg, education and income. The Population Education Registry contains information on nearly all adult Danes and provides the highest completed level of education, defined as the longest duration of schooling.

The Danish Civil Registration System contains data on addresses, migration, and date of death. This system allowed us to extract population controls and to keep track of all persons during the study period.

Supplemental Table I. Codes and definitions

Category	Coding system	Definition
Merkel cell carcinoma	ICD-10	C44.0-C44.9
	Morphology code	8246/3 Neuroendocrine carcinoma, NOS
		8247/3 Merkel cell carcinoma
Malignant adnexal skin tumors	ICD-10	C44.0-C44.9
	Morphology code	8110/3 Pilomatrix carcinoma
		8200/3 Adenoid cystic carcinoma
		8390/3 Skin appendage carcinoma
		8400/3 Sweat gland adenocarcinoma
		8401/3 Apocrine adenocarcinoma
		8402/3 Nodular hidradenoma, malignant
		8407/3 Sclerosing sweat duct carcinoma
		8409/3 Eccrine poroma, malignant
		8410/3 Sebaceous adenocarcinoma
		8413/3 Eccrine adenocarcinoma
		8480/3 Mucinous adenocarcinoma
		8542/3 Pagets disease, extramammary
		8940/3 Mixed tumor, malignant, NOS
Exclusion criteria		
Any cancer	ICD-10	C00-97
Organ transplant	ICD-10	Z94 (except Z94.5 and Z94.7)
	NCSP-code	KFQA, KFQB, KGDG, KJJC, KJLE, KKAS
Azathioprine	ATC code	L04AX01
Cyclosporine	ATC code	L04AD01
Mycophenolate mofetil		L04AA06
HIV	ICD-10	B20-24 and Z21
Use of drugs (≥2 prescriptions before index date)		
HCTZ-containing drugs		
HCTZ	ATC code	C03AA03
HCTZ and potassium	ATC code	C03AB
HCTZ and amiloride	ATC code	C03EA01
HCTZ and angiotensin II antagonist	ATC code	C09DA01, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08
HCTZ and ACE inhibitor	ATC code	C09BA02, C09BA03, C09BA05
HCTZ/calcium antagonist/angiotensin II antagonist	ATC code	C09DX01
HCTZ/metoprolol	ATC code	C07BB02
Other antihypertensive drugs		
ACE inhibitors	ATC code	C09A, C09B
Angiotensin II antagonists	ATC code	C09C, C09D
Calcium-channel blockers	ATC code	C08CA (ex C08CA05)
Drugs with similar indication as HCTZ and potential photosensitizing effects		
Furosemide	ATC code	C03CA01
Bendroflumethiazide	ATC code	C03AA01, C03AB01
Other photosensitizing drugs		
Topical retinoids	ATC code	D10AD
Oral retinoids	ATC code	D05BB D10BA01
Tetracycline	ATC code	J01AA07
Macrolides	ATC code	J01FA
Aminoquinolines	ATC code	P01BA
Amiodarone	ATC code	C01BD01
Methoxypsoralene	ATC code	D05AD, D05BA
PUVA	Procedure code	BNGA1

Continued

Supplemental Table I. Cont'd

Category	Coding system	Definition
Other		
Low-dose aspirin	ATC code	B01AC06, B01AC30, N02BA01, and N02BA51
Non-aspirin NSAIDs	ATC code	M01A excl. M01AX
Statins	ATC code	C10AA
Prior diagnoses (diagnostic code or drug marker)		
Heavy alcohol consumption	ICD-8	291, 303, 425.5, 537.5, 571.0, 571.1, 571.2, 571.3, 577.10
	ICD-10	G31.2, G62.1, G72.1, I42.6, F10.2, K70, K86.0
	ATC code	N07BB
Diabetes	ICD-8	249.00, 249.09, 250.00, 250.09
	ICD-10	E10-E14
	ATC code	A10
Chronic obstructive pulmonary disease	ICD-8	490.00 491.00 491.01 491.03
	ICD-10	J42-J44
	ATC code	R03BB
Actinic keratosis	ICD-10	L57.0
Psoriasis	ICD-10	L40
	ATC code	D05AX
Atopic dermatitis	ICD-10	L20
Chronic renal insufficiency	ICD-10	E102, E112, E122, E132, E142, I12 (÷I129), N01, N03, N083, N085, N118C, N14, N150, N16 (÷N160), N18 (÷N181), N19, N26, P960, Q601, Q602, Z992
Education		
Short	Duration	10 years
Medium	Duration	11-13 years
Long	Duration	>13 years
Unknown	Duration	—

ACE, Angiotensin-converting enzyme; *ATC*, Anatomical Therapeutic Chemical; *HCTZ*, hydrochlorothiazide; *ICD*, International Classification of Disease; *NCSP*, Nordic Classification of Surgical Procedures; *NSAID*, nonsteroidal anti-inflammatory drug; *PUVA*, psoralen and ultraviolet A phototherapy.

Supplemental Table II. Association between exposure to bendroflumethiazide and risk for Merkel cell carcinoma or malignant adnexal skin tumors

Subgroup	Cases	Controls	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Merkel cell carcinoma				
Nonuse	52	1138	1.0 (referent)	1.0 (referent)
Ever use	45	719	1.3 (0.9-2.1)	1.1 (0.7-1.8)
High use, ≥50,000 mg	13	201	1.1 (0.6-2.2)	0.9 (0.4-1.9)
Cumulative amount, mg				
1-49,999	32	518	1.4 (0.9-2.3)	1.2 (0.7-2.1)
50,000-99,999	8	136	0.9 (0.4-2.1)	0.8 (0.3-2.0)
≥100,000	5	65	1.3 (0.5-3.5)	1.0 (0.3-3.2)
Malignant adnexal skin tumor				
Nonuse	101	1853	1.0 (referent)	1.0 (referent)
Ever use	31	767	0.7 (0.4-1.1)	0.6 (0.4-1.0)
High use	8	211	0.6 (0.3-1.3)	0.5 (0.2-1.3)
Cumulative amount, mg				
1-49,999	23	556	0.7 (0.4-1.1)	0.6 (0.4-1.1)
50,000-99,999	n < 5	141	—	—
≥100,000	n < 5	70	—	—

CI, Confidence interval; *OR*, odds ratio.

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

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

Supplemental Table III. Association between exposure to furosemide and risk for Merkel cell carcinoma or malignant adnexal skin tumors

Subgroup	Cases	Controls	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Merkel cell carcinoma				
Nonuse	59	1485	1.0 (referent)	1.0 (referent)
Ever use	38	372	2.6 (1.6-4.0)	1.6 (0.9-2.6)
High use, ≥2000 DDD	17	111	3.7 (2.0-6.9)	1.9 (0.9-4.0)
Cumulative amount, DDD				
1-999	21	261	2.0 (1.2-3.5)	1.3 (0.7-2.4)
1000-4999	8	46	4.6 (2.0-10.8)	2.1 (0.7-6.2)
≥5000	9	65	3.7 (1.6-8.4)	2.0 (0.7-5.2)
Malignant adnexal skin tumor				
Nonuse	117	2208	1.0 (referent)	1.0 (referent)
Ever use	15	412	0.6 (0.3-1.1)	0.5 (0.3-1.0)
High use	n < 5	115	—	—
Cumulative amount, DDD				
1-999	11	297	0.7 (0.4-1.3)	0.6 (0.3-1.1)
1000-4999	n < 5	72	—	—
≥5000	n < 5	43	—	—

CI, Confidence interval; *DDD*, defined daily doses; *OR*, odds ratio.

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

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

Supplemental Table IV. Association between exposure to calcium channel blockers and risk for Merkel cell carcinoma or malignant adnexal skin tumors

Subgroup	Cases	Controls	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Merkel cell carcinoma				
Nonuse	70	1421	1.0 (referent)	1.0 (referent)
Ever use	27	436	1.2 (0.7-1.9)	0.9 (0.5-1.6)
High use, ≥2000 DDD	9	153	1.2 (0.6-2.5)	0.9 (0.4-2.1)
Cumulative amount, DDD				
1-999	18	283	1.2 (0.7-2.1)	1.0 (0.5-1.9)
1000-4999	5	84	1.2 (0.5-3.3)	0.9 (0.3-2.7)
≥5000	n < 5	69	—	—
Malignant adnexal skin tumor				
Nonuse	103	2155	1.0 (referent)	1.0 (referent)
Ever use	29	465	1.3 (0.9-2.1)	1.3 (0.8-2.1)
High use	10	161	1.4 (0.7-2.9)	1.0 (0.5-2.2)
Cumulative amount, DDD				
1-999	19	304	1.3 (0.8-2.3)	1.4 (0.8-2.5)
1000-4999	8	94	2.0 (0.9-4.3)	1.6 (0.7-3.6)
≥5000	n < 5	67	—	—

CI, Confidence interval; *DDD*, defined daily doses; *OR*, odds ratio.

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

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

Supplemental Table V. Association between exposure to angiotension-converting enzyme inhibitors and risk for Merkel cell carcinoma or malignant adnexal skin tumors

Subgroup	Cases	Controls	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Merkel cell carcinoma				
Nonuse	59	1324	1.0 (referent)	1.0 (referent)
Ever use	38	533	1.7 (1.1-2.6)	1.3 (0.8-2.2)
High use, ≥2000 DDD	16	181	2.0 (1.1-3.7)	1.3 (0.6-2.6)
Cumulative amount, DDD				
1-999	22	352	1.5 (0.9-2.6)	1.2 (0.7-2.2)
1000-4999	7	87	2.0 (0.8-4.6)	2.1 (0.8-5.4)
≥5000	9	94	2.1 (0.9-4.7)	0.6 (0.2-1.9)
Malignant adnexal skin tumor				
Nonuse	97	1980	1.0 (referent)	1.0 (referent)
Ever use	35	640	1.1 (0.7-1.7)	1.0 (0.6-1.6)
High use	12	226	1.0 (0.5-2.1)	0.9 (0.4-1.9)
Cumulative amount, DDD				
1-999	23	414	1.1 (0.7-1.8)	1.0 (0.6-1.7)
1000-4999	n < 5	118	—	—
≥5000	9	108	1.6 (0.7-3.4)	1.1 (0.4-2.9)

CI, Confidence interval; *DDD*, defined daily doses; *OR*, odds ratio.

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

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

Supplemental Table VI. Association between exposure to angiotensin II receptor antagonists and risk for Merkel cell carcinoma or malignant adnexal skin tumors

Subgroup	Cases	Controls	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Merkel cell carcinoma				
Nonuse	77	1525	1.0 (referent)	1.0 (referent)
Ever use	20	332	1.2 (0.7-2.0)	0.8 (0.4-1.5)
High use, ≥2000 DDD	9	141	1.2 (0.6-2.5)	0.6 (0.2-1.5)
Cumulative amount, DDD				
1-999	11	191	1.0 (0.5-2.0)	1.0 (0.5-2.2)
1000-4999	5	96	1.0 (0.4-2.5)	0.5 (0.2-1.6)
≥ 5000	n < 5	45	—	—
Malignant adnexal skin tumor				
Nonuse	108	2286	1.0 (referent)	1.0 (referent)
Ever use	24	334	1.5 (0.9-2.4)	1.7 (1.0-3.0)
High use	6	126	1.1 (0.4-2.5)	1.0 (0.4-2.9)
Cumulative amount, DDD				
1-999	18	208	1.8 (1.0-3.1)	2.0 (1.1-3.7)
1000-4999	6	86	1.5 (0.6-3.7)	1.5 (0.6-4.2)
≥ 5000	n < 5	40	—	—

CI, Confidence interval; *DDD*, defined daily doses; *OR*, odds ratio.

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

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

Supplemental Table VII. Effect of choice of lag time* on the association between high use (≥50,000 mg) of hydrochlorothiazide and risk for Merkel cell carcinoma or malignant adnexal skin tumors

Merkel cell carcinoma		Malignant adnexal skin tumor	
Lag time, months	**Adjusted OR (95% CI)**	**Lag time, months**	**Adjusted OR (95% CI)**
0	1.9 (0.9-4.1)	0	3.3 (1.7-6.2)
6	2.1 (1.0-4.5)	6	3.5 (1.8-6.7)
12	2.2 (1.0-4.8)	12	3.6 (1.9-6.8)
18	2.3 (1.1-4.8)	18	3.3 (1.7-6.5)
24	2.2 (1.1-4.8)	24	3.6 (1.9-7.0)
30	1.9 (0.8-4.4)	30	3.8 (2.0-7.4)
36	2.0 (0.9-4.4)	36	4.1 (2.1-8.0)
42	2.1 (0.9-4.9)	42	4.5 (2.3-8.9)
48	2.4 (1.0-5.4)	48	4.4 (2.2-8.7)
54	2.5 (1.1-5.7)	54	5.4 (2.7-10.8)
60	2.5 (1.1-5.9)	60	5.6 (2.8-11.3)

CI, Confidence interval; *OR*, odds ratio.

*Lag time refers to the period before the index date that is ignored with respect to drug exposure. A lag time of 24 months corresponds to the main analysis.