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Capsule summary

What is already known on this topic

Hydrochlorothiazide has photosensitizing properties and has been linked to non-melanoma skin cancer.

What this article adds to our knowledge

We found evidence of a positive dose-response relationship for cumulative use of hydrochlorothiazide and risk of Merkel cell carcinoma and malignant adnexal skin tumors.

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

Use of hydrochlorothiazide should be carefully considered in patients at high risk for skin cancer.

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

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

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

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Abstract

Background

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

Objective

To examine the association between hydrochlorothiazide use and the risk of MCC and MAST.

Methods

Using Danish nationwide health registries, we identified all patients with incident MCC or MAST during 2004–2015 and matched cases individually to cancer-free population controls by risk set sampling. Using conditional logistic regression, we estimated odds ratios (ORs) 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, increasing to 3.3 (95% CI 1.3-8.3) and 5.6 (95% CI 2.4-13.3) with highest use (≥100,000mg). We found no increase in risk of the tumors in analyses of drugs with similar indications as hydrochlorothiazide, except a tendency toward an increased risk of MCC associated with use of furosemide (OR 1.9, 95% CI 0.9-4.0).

Limitations

No data on sun exposure was available.

Conclusions

Hydrochlorothiazide use is associated with an increased risk of MCC and MAST.

Key words

Hydrochlorothiazide, antihypertensives, skin cancer, Merkel cell carcinoma, malignant adnexal skin tumors, pharmacology, epidemiology

Introduction

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 of lip cancer, non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) and melanoma. [4–6]

Considering the shared risk factor of ultraviolet radiation, drug photosensitivity could also be implicated in the development of other rarer types of non-melanoma skin cancer, e.g., 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 that 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 increasing age, light skin type, ultraviolet radiation and immunosuppression. A polyomavirus has been found in the genome of 80 % of Merkel cell carcinomas.[10] While the aetiology of malignant adnexal skin tumors is less elucidated, similar risk factors have been suggested (except for emergence of polyomavirus), including ultraviolet radiation..[11–14]

Despite the involvement of ultraviolet radiation in the aetiology and pathogenesis of Merkel cell carcinoma and malignant adnexal skin tumors, only few previous studies have examined the effect of photosensitizing drug use on the risk of these tumors. To our knowledge, only one study has examined the association between use of diuretics and risk of 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 of Merkel cell carcinoma and malignant adnexal skin tumors.

Methods

We performed a nested case-control study, similarly to our recent studies [4–6], based on the nationwide Danish demographic and health registries (described in detail in **Appendix A**).

From the Danish Cancer Registry [16], we identified patients (cases) with a histologically verified first primary diagnosis of Merkel cell carcinoma or malignant adnexal skin tumor between 1 January 2004 and 31 December 2015 (study period). **Appendix B** 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 cases to have resided in Denmark for at least 10 consecutive years prior to index date, and to have no previous records of cancer, organ transplantation, human immunodeficiency virus, and 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 for cases. Controls were allotted the same index date as their corresponding cases.

We retrieved prescription data from 1995 to two years before the index date for both cases and controls. Ever use of hydrochlorothiazide was defined as having redeemed at least one 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 subjects. Based on this information, we could estimate each person's cumulative use of hydrochlorothiazide.

Main analyses

We used conditional logistic regression to calculate minimal (age and gender 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 topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, methoxypsoralene, and amiodarone; b) aspirin, non-aspirin non-steroidal 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 (i.e., primarily mild to moderate hypertension), including ACE inhibitors, angiotensin II-receptor blockers (ARBs), and group 2 calcium channel blockers. In the analyses of other diuretics and non-diuretic antihypertensives, we adjusted odds ratios 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 above); low comorbidity (Charlson Comorbidity Index score=0); no history of diabetes or chronic renal insufficiency, as patients with diabetes or renal insufficiency are known to have an overall increased risk of cancer; no history of actinic keratosis, which is associated with exposure to UV light and considered a precursor of non-melanoma skin cancer; and no history of atopic dermatitis or psoriasis, which is associated with exposure to UV light and possibly associated with non-melanoma skin cancer risk. [20,21] Finally we repeated the main analyses, varying the lag time between 0 and 5 years (in steps of 6 months).

147 **Ethical Approval**

148 The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study. According to
149 Danish law, ethical approval is not required for registry-based studies.

150

151 **Other**

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

153

Results

We included 97 cases of Merkel cell carcinoma and 132 cases of malignant adnexal skin tumors (**Figure 1**) matched to 1,857 and 2,620 population controls, respectively. Baseline characteristics were similar among cases of malignant adnexal skin tumor cases and controls (**Table 1**); however, Merkel cell carcinoma cases had higher comorbidity and drug use, in particular of the photosensitizing drugs macrolides and aminoquinolines, and had higher level of education compared with their controls.

We observed high use of hydrochlorothiazide among 11.3% of Merkel cell carcinoma cases compared with 4.7% of controls, yielding an OR of 2.3 (95% CI; 1.1-4.8). The corresponding figures for malignant adnexal skin tumor cases and controls were 9.8% and 2.8%, respectively, equivalent to an OR of 3.6 (95% CI; 1.9-7.0) **(Table 2)**.

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, $p<0.01$) for Merkel cell carcinoma and 5.6 (95% CI 2.4-13.3) (test for trend, $p<0.01$) for malignant adnexal skin tumors in the highest exposure category (≥100,000 mg) **(Table 2)**.

Analyses restricted to individuals with no recorded use of photosensitizing drugs other than hydrochlorothiazide had little impact 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 of Merkel cell carcinoma or malignant adnexal skin tumors in analyses of drugs with similar indications as hydrochlorothiazide **(Supplementary results Ia-Ig)**, except a tendency toward an increased risk of Merkel cell carcinoma associated with use of furosemide (OR 1.9, 95%CI 0.9-4.0). **(Supplementary results Ib)**.

Finally, we observed increasing ORs with increasing lag time for hydrochlorothiazide use **(Supplementary Results II)**

Discussion

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

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

Evidence is very sparse on photosensitizing drugs and risk of Merkel cell carcinoma or malignant adnexal skin tumors. A previous Danish study by Kaae *et al* [15] investigated the association between photosensitizing diuretics and risk of Merkel cell carcinoma, but did not include hydrochlorothiazide in their analyses. Noteworthy, similar to the finding in our study, Kaae *et al* also observed a moderately increased risk of 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 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 non-melanoma and melanoma skin cancer risk [4–6], the present findings

indicate that use of hydrochlorothiazide is associated with increased risk of all types of UV-light associated skin cancer. If this indeed is the case, UV-light exposure can be considered an effect modifier of the association between Merkel cell carcinoma and malignant adnexal skin tumors, and hydrochlorothiazide. 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 of local, regional and distant recurrence. A large study of Merkel cell carcinoma from United States reported a five-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 carcinomas and malignant adnexal skin tumors. Our results suggest that avoidance of hydrochlorothiazide use may contribute to this.

In conclusion, our study indicates that use of hydrochlorothiazide increases the risk of Merkel cell carcinomas and malignant adnexal skin tumors.

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

280 [1]Azathioprine, cyclosporine, and mycophenolate mofetil.

281 Abbrevations: MCC = Merkel cell carcinoma, MAST = malignant adnexal skin tumor.

282

283 # Table 1

284 Characteristics of cases with Merkel cell carcinoma or malignant adnexal skin tumor and their matched controls

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	Merkel cell carcinoma		Malignant adnexal skin tumor	
	Cases (n=97)	**Controls** (n=1,857)	**Cases** (n=132)	**Controls** (n=2,620)
Median age (IQR), years	80 (70-87)	79 (70-86)	73 (61-79)	73 (61-79)
Male gender	38 (39.2%)	760 (40.9%)	63 (47.7%)	1,240 (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%)	1,064 (57.3%)	81 (61.4%)	1,399 (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	5 (5.2%)	28 (1.5%)	(n<5)	36 (1.4%)
CCI score				
0	43 (44.3%)	1,132 (61.0%)	87 (65.9%)	1,707 (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%)	1,044 (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.
HCTZ = Hydrochlorothiazide
IQR = Interquartile range
CCI = Charlson Comorbidity Index

286 **Table 2**

287 Association between exposure to hydrochlorothiazide and risk of Merkel cell carcinoma and malignant adnexal
288 skin tumor

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Subgroup	Cases	Controls	Adjusted OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Merkel cell carcinoma	(n=97)	(n=1,857)		
Non-use	77	1,549	1.0 (ref.)	1.0 (ref.)
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				
1-49,999 mg	9	221	0.9 (0.4-1.8)	0.6 (0.3-1.3)
50,000-99,999 mg	(n<5)	45	(-)	(-)
≥ 100,000 mg	7	42	3.7 (1.6-8.7)	3.3 (1.3-8.3)
Malignant adnexal skin tumor	(n=132)	(n=2,620)		
Non-use	111	2,311	1.0 (ref.)	1.0 (ref.)
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				
1-49,999 mg	8	236	0.7 (0.4-1.6)	0.7 (0.4-1.6)
50,000-99,999 mg	5	46	2.3 (0.9-6.1)	2.4 (0.9-6.5)
≥ 100,000 mg	8	27	5.8 (2.5-13.3)	5.6 (2.4-13.3)

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

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

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