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LETTER TO THE EDITOR

No association between hydrochlorothiazide use and uveal melanoma

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The antihypertensive agent hydrochlorothiazide possesses photosensitizing properties [1, 2] and has recently been associated with an increased risk of non-melanoma skin cancer (NMSC), in particular squamous cell carcinoma [3–5]. In a subsequent study, use of hydrochlorothiazide was also found to be associated with cutaneous malignant melanoma [7]. This association was seemingly driven by the subtypes nodular melanoma and lentigo melanoma. The photosensitizing properties of hydrochlorothiazide [6] align well with these findings as the main risk factor for lentigo melanomas is adult UV exposure [8]. The association between hydrochlorothiazide and lentigo melanoma has later been replicated in two independent studies (*currently undergoing review*). Whether hydrochlorothiazide use is also associated with increased risk of intraocular uveal melanoma is unknown. Uveal melanoma is the most common intraocular tumour in adults and is comprised of melanomas of the choroid, ciliary corpus, and iris. Sun exposure is associated with increased risk of uveal melanoma, and the incidence of uveal melanoma is highest in populations with light skin types [9]. This prompted us to assess the association between hydrochlorothiazide use and uveal melanoma.

We performed a nationwide Danish case-control study, applying similar methodology as described previously [3, 4]. In brief, we identified histologically verified cases of uveal melanoma 2004–2015 using the Danish Cancer Registry [10]. For each case, we identified 10 population controls matched on age and sex. We excluded cases and controls aged below 18 or above 90 years; with recent migrations; a history of organ transplantation; use of azathioprine, cyclosporine, or mycophenolate mofetil; and HIV/AIDS diagnoses. Use of hydrochlorothiazide and other drugs was obtained from the Danish Prescription Registry [11], and covariates were assessed using data from the Danish National Patient Registry [12] and Danish Education Registries [13]. As recent exposure is unlikely to influence uveal melanoma risk, we disregarded exposure the 2 years preceding the index date. Odds ratios (OR) associating use of hydrochlorothiazide with uveal melanoma were estimated using conditional logistic regression, adjusting for covariates (see Table 1). A pre-specified primary exposure metric of 'long-term' hydrochlorothiazide use was defined as cumulative use of ≥ 50,000 mg. Supplementary analyses were performed for bendroflumethiazide and ACE inhibitors as negative control exposures. The applied statistical code and exposure, covariate, and outcome definitions can be provided upon request to the corresponding author.

We identified 514 eligible cases of uveal melanoma (median age 63; 49% women), of whom 12% (n = 60) had ever used hydrochlorothiazide and 2.3% (n = 12) were classified as 'long-term' users. The corresponding proportions among controls were 11% and 1.8%. This yielded an adjusted OR for ever use of 1.1 (95%CI 0.8–1.5) and 1.2 (95%CI 0.6–2.2) for long-term use (Table 1), with no apparent dose-response pattern (p = 0.17). Applying various lag-times and restricting to subgroups without history of diabetes or previous cancer had no effect on the estimates (data not shown). Long-term uses of bendroflumethiazide and ACE inhibitors were associated with uveal melanoma with an OR of 1.0 (95%CI 0.6–1.5) and 1.4 (95%CI 0.9–2.1), respectively.

The principal strength of the present study is the use of nationwide registries of high validity that allowed for capture of histologically verified uveal melanoma cases and risk-set sampling of controls with low risk of selection bias. We cannot rule out an increased risk of uveal melanoma associated with hydrochlorothiazide as reflected by the upper limit of the confidence interval of 2.2. However, we found no evidence of

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Table 1 Association between exposure to hydrochlorothiazide and risk of uveal melanoma, according to cumulative amount of hydrochlorothiazide use

	Cases	Controls	Crude OR[a]	Adjusted OR[b]
Non-use	454	4566	1.0 (ref.)	1.0 (ref.)
Ever use	60	574	1.1 (0.8–1.4)	1.1 (0.8–1.5)
High use (≥ 50,000 mg)	12	94	1.2 (0.6–2.2)	1.2 (0.6–2.2)
Cumulative amount				
10,000–24,999 mg	35	348	1.0 (0.7–1.5)	1.0 (0.7–1.5)
25,000–49,999 mg	13	132	1.0 (0.5–1.7)	1.0 (0.6–1.9)
50,000–99,999 mg	6	49	1.2 (0.5–2.9)	1.1 (0.5–2.7)
≥ 100,000 mg	6	45	1.2 (0.5–2.8)	1.3 (0.5–3.1)
Incremental (/10,000 mg)	60	574	1.0 (1.0–1.1)	1.0 (1.0–1.1)

[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, topical or systemic psoralens, tetracycline, macrolides, fluoroquinolones, aminoquinolines, and amiodarone; (b) aspirin, non-aspirin non-steroidal anti-inflammatory drugs, systemic glucocorticoids, immunosuppressants, and statins; (c) history of heavy alcohol consumption, diabetes, chronic kidney disease, and chronic obstructive pulmonary disease; (d) history of non-melanoma skin cancer; (e) Charlson Comorbidity Index score (0: low; 1–2: medium; or ≥ 3: high); and (f) highest achieved education (short, medium, long, or unknown)

a dose-response pattern and observed similar associations for bendroflumethiazide and ACE inhibitors. In conclusion, we found no evidence of an association between use of hydrochlorothiazide and risk of uveal melanoma.

Compliance with ethical standards

Conflict of interest Anton Pottegård declares that he has received funding from LEO Pharma (the Danish manufacturer of bendroflumethiazide) for unrelated projects, all paid to the institution where he is employed. The remaining authors report no conflict of interest.

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