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Letters

RESEARCH LETTER

Association of Hydrochlorothiazide Use and Risk of Malignant Melanoma

We have recently shown that hydrochlorothiazide use increases the risk of lip and nonmelanoma skin cancer, notably squamous cell carcinoma.[1,2] It would have substantial implications if the carcinogenic effect of hydrochlorothiazide also extended to malignant melanoma.

Methods | Similarly to our recent studies of hydrochlorothiazide,[1,2] we identified histologically verified melanoma cases (January 2004 to December 2015), each matched 1:10 (risk-set sampling; age, sex, and date) to cancer-free population controls. We required cases and controls to be between ages 18 and 90 years, without previous history of cancer (except nonmelanoma skin cancer), organ transplantation, HIV infection, or azathioprine use, and to have resided continuously in Denmark for 10 years.

Using conditional logistic regression, we calculated odds ratios (ORs), with 95% CIs, for melanoma associated with cumulative hydrochlorothiazide use compared with never-use, adjusting for potential confounders (**Table 1** and **2**). We performed stratified analyses by localization, stage, histologic subtype, and subgroups of age, sex, and history of nonmelanoma skin cancer. To evaluate potential confounding by indication, we performed analyses for other antihypertensive drugs, including bendroflumethiazide, angiotensin-converting enzyme inhibitors, angiontensin-II receptor antagonists, and calcium-channel blockers. This study was approved by Statistics Denmark and the Danish Data Protection Agency.

Results | We identified 22 010 cases of melanoma. After exclusions, the final study population comprised 19 273 cases and 192 730 population controls. Cases had slightly lower comorbidity, higher educational level, and higher prevalence of previous nonmelanoma skin cancer than controls. Remaining characteristics were similar between cases and controls.

Overall, 413 cases (2.1%) and 3406 controls (1.8%) were classified as high-users (≥50 000 mg) of hydrochlorothiazide, yielding an adjusted OR of 1.22 (95% CI, 1.09-1.36) for melanoma. No clear dose-response pattern emerged between hydrochlorothiazide use and melanoma risk (Table 1). Analyses by melanoma localization, stage, age, sex, and history of nonmelanoma skin cancer yielded results comparable to the main analysis (data not shown). When stratifying by histological subtype (Table 2), higher ORs occurred for nodular melanoma (n = 1695 cases [8.8%]; OR, 2.05; 95% CI, 1.54-2.72; *P* for trend = .01) and lentigo melanoma (n = 500 cases [2.6%]; OR, 1.61; 95% CI, 1.03-2.50; *P* for trend = .16) than for superficial spreading melanoma (n = 13 781 cases [72%]; OR, 1.11; 95% CI, 0.97-1.27; *P* for trend = .73).

In secondary analyses, we observed associations close to the null for overall melanoma risk with long-term use of bendroflumethiazide (OR, 1.10; 95% CI, 1.02-1.19; *P* for trend = 0.47), angiotensin-converting enzyme inhibitors (OR, 1.07; 95% CI, 0.99-1.16; *P* for trend = .53), angiotensin-II receptor antagonists (OR, 1.18; 95% CI, 1.07-1.29; *P* for trend = .07), and calcium-channel blockers (OR, 1.06; 95% CI, 0.97-1.14; *P* for trend = .94). These associations remained neutral in subanalyses stratified by melanoma subtype (data not shown).

Table 1. Association of Exposure to Hydrochlorothiazide and Risk of Malignant Melanoma

Use and Dose	Cases, No. (n = 19 273)	Controls, No. (n = 192 730)	Adjusted OR (95% CI)	
			Model 1[a]	Model 2[b]
Hydrochlorothiazide				
Never used	17 315	175 486	1 [Reference]	1 [Reference]
Ever used	1958	17 244	1.16 (1.11-1.22)	1.17 (1.11-1.23)
High use (≥50 000 mg)	413	3406	1.24 (1.12-1.38)	1.22 (1.09-1.36)
Cumulative dose				
1-24 999 mg	1160	10 483	1.14 (1.07-1.21)	1.14 (1.07-1.22)
25 000-49 999 mg	385	3355	1.18 (1.06-1.32)	1.18 (1.05-1.32)
50 000-99 999 mg	219	1852	1.22 (1.06-1.41)	1.21 (1.05-1.40)
≥100 000 mg	194	1554	1.26 (1.08-1.46)	1.21 (1.04-1.42)
Test for trend	1958	17 244	*P* = .24	*P* = .42

[a] Adjusted for age, sex, and calendar time (by use of risk-set matching and conditional analysis).

[b] Fully adjusted model additionally adjusted for history of nonmelanoma skin cancer, other comorbidity (diabetes, chronic obstructive pulmonary disease, alcohol abuse–associated disorders, chronic renal failure), Charlson Comorbidity Index score (0, low; 1-2, medium; or ≥3, high), use of certain drugs (topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, methoxypsoralen, low-dose aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, statins, or oral steroids), and highest achieved education (short, medium, long, or unknown).

Table 2. Association of Exposure to Hydrochlorothiazide and Risk of Malignant Melanoma According to Amount of Hydrochlorothiazide Use and Specified by Melanoma Subtype

Melanoma	Cases. No.	Controls, No.	Adjusted OR (95% CI)	
			Model 1[a]	Model 2[b]
Superficial Spreading Melanoma				
Never used	12 494	126 216	1 [Reference]	1 [Reference]
Ever used	1287	11 594	1.13 (1.06-1.20)	1.13 (1.06-1.20)
High use (≥50 000 mg)	254	2268	1.14 (0.99-1.30)	1.11 (0.97-1.27)
Cumulative dose				
1-24 999 mg	783	7023	1.14 (1.05-1.23)	1.13 (1.05-1.23)
25 000-49 999 mg	250	2303	1.11 (0.97-1.27)	1.10 (0.96-1.27)
50 000-99 999 mg	140	1252	1.15 (0.96-1.38)	1.14 (0.95-1.37)
≥100 000 mg	114	1016	1.12 (0.91-1.36)	1.06 (0.87-1.30)
Test for trend	1287	11 594	*P* = .94	*P* = .73
Nodular Melanoma				
Never used	1465	15 108	1 [Reference]	1 [Reference]
Ever used	230	1842	1.31 (1.12-1.53)	1.28 (1.09-1.49)
High use (≥50 000 mg)	68	351	2.13 (1.61-2.80)	2.05 (1.54-2.72)
Cumulative dose				
1-24 999 mg	119	1142	1.08 (0.88-1.32)	1.05 (0.86-1.29)
25 000-49 999 mg	43	349	1.24 (0.90-1.72)	1.17 (0.84-1.64)
50 000-99 999 mg	34	195	1.90 (1.30-2.78)	1.81 (1.23-2.67)
≥100 000 mg	34	156	2.34 (1.59-3.45)	2.26 (1.52-3.36)
Test for trend	230	1842	*P* = .01	*P* = .01
Lentigo Melanoma				
Never used	386	4198	1 [Reference]	1 [Reference]
Ever used	114	802	1.57 (1.25-1.97)	1.58 (1.25-2.00)
High use (≥50 000 mg)	28	177	1.72 (1.13-2.62)	1.61 (1.03-2.50)
Cumulative dose				
1-24 999 mg	58	476	1.32 (0.98-1.78)	1.35 (0.99-1.83)
25 000-49 999 mg	28	149	2.22 (1.44-3.43)	2.30 (1.46-3.60)
50 000-99 999 mg	11	99	1.25 (0.66-2.38)	1.09 (0.56-2.11)
≥100 000 mg	17	78	2.26 (1.30-3.91)	2.24 (1.25-3.99)
Test for trend	114	802	*P* = .11	*P* = .16

[a] Adjusted for age, sex, and calendar time (by use of risk-set matching and conditional analysis).

[b] Fully adjusted model additionally adjusted for history of nonmelanoma skin cancer, other comorbidity (diabetes, chronic obstructive pulmonary disease, alcohol abuse associated disorders, chronic renal failure), Charlson Comorbidity Index score (0, low; 1-2, medium; or ≥3, high), use of certain drugs (topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, methoxypsoralen, low-dose aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, statins, or oral steroids), and highest achieved education (short, medium, long, or unknown).

Discussion | The main strength of our study is the use of high-quality nationwide registry data.[3] The main limitations are a lack of information on risk factors such as sun exposure, skin pigmentation, and family history of melanoma. However, these characteristics are unlikely to be substantially associated with hydrochlorothiazide use, and thus unlikely to confound out estimates.

Thiazide use and melanoma risk has been investigated in a few previous studies; however, only 2 studies,[4,5] both from northern Denmark, have specifically examined hydrochlorothiazide. The first study reported an OR of 1.32 (95% CI, 1.03-1.70) for melanoma risk overall associated with 10 000 mg increments of hydrochlorothiazide.[4] The corresponding OR for hydrochlorothiazide in combination with amiloride was 1.43 (95% CI, 1.09-1.88).[4] The other study found no association between hydrochlorothiazide use combined with amiloride and melanoma risk (OR, 1.02; 95% CI, 0.78-1.33).[5] Neither of these studies included dose-response or histology-specific analyses.

The findings for melanoma subtype are somewhat surprising, as lentigo and superficial spreading melanoma are known to be associated with high sun exposure, whereas the etiology of nodular melanomas is less elucidated.[6] It is worrying that hydrochlorothiazide use appears to be associated with an increased risk of melanoma, and the particular associations observed for lentigo melanoma and nodular melanoma warrant further research.

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Drafting of the manuscript: Pottegård, Pedersen, Gaist.
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LESS IS MORE

Use of Venous Thromboembolism Prophylaxis in Hospitalized Patients

National guidelines[1] recommend objective risk stratification for venous thromboembolism (VTE) in hospitalized medical patients. The Padua Prediction Score risk assessment model[2] is recommended to categorize patients as high or low risk. The Michigan Hospital Medicine Safety Consortium (HMS), a statewide quality collaborative aimed at preventing adverse events in hospitalized medical patients, collects detailed data on VTE risk factors, prophylactic treatment, and outcomes. Using data from the HMS,[3] we sought to determine whether patients in this cohort were receiving appropriate VTE prophylaxis.

Methods | Patients admitted to a non–intensive care medicine unit for 2 or more days were eligible for inclusion; data were collected through a standardized process at each hospital. Using the Padua Prediction Score risk assessment model,[2] we categorized patients on admission as low or high risk for VTE events. For high-risk patients, contraindications to pharmacologic prophylaxis were assessed. Excessive VTE prophylaxis was defined as pharmacologic or mechanical prophylaxis for low-risk patients, pharmacologic prophylaxis for high-risk patients with a contraindication to anticoagulation, and the combination of pharmacologic and mechanical prophylaxis in all cases. Underuse of VTE prophylaxis was defined as no pharmacologic prophylaxis in high-risk patients without a contraindication to anticoagulation and no prophylaxis (pharmacologic or mechanical) in high-risk patients with a contraindication to anticoagulation. Appropriate pharmacologic prophylaxis included any of the following on day 1 and/or day 2 of the index hospitalization: heparin, 5000 U twice daily; heparin, 5000 U 3 times daily; heparin, 7500 U 3 times daily (for morbid obesity); enoxaparin, 40 mg/d; enoxaparin, 30 mg/d (for creatinine clearance <30 mL/min); enoxaparin, 30 mg twice daily; dalteparin, 5000 U daily; or fondaparinux 2.5 mg/d. The HMS-defined contraindications include any of the following: bleeding present upon hospital admission; intracranial hemorrhage within the past year; other hemorrhage within the last 6 months; coagulopathy, hemophilia, or other significant bleeding disorder; and platelet levels lower than $50 \times 10^3/\mu L$ (to convert to $\times 10^9$ per liter, multiply by 1.0). Hospitals were rank ordered according to rates of excess VTE prophylaxis across low- and high-risk patients and rates of underuse of VTE prophylaxis in high-risk patients. Rank of hospital excess use and underuse of VTE prophylaxis were compared using a Pearson correlation coefficient.

Excessive VTE prophylaxis was assessed using descriptive variables. Odds ratios, 95% CIs, and *P* values for excess prophylaxis were calculated using logistic generalized estimating equation models, accounting for hospital clustering. Findings were considered significant at $P < .05$. Because the purpose of the HMS is to measure and improve the quality of existing medical practice, this project received a "not regulated" status by the University of Michigan Medical School institutional review board.

Results | Between January 1, 2015, and December 21, 2016, data were collected on 44 775 eligible patients across 52 Michigan hospitals. Mean (SD) patient age was 64.7 (18.4) years; 24 742 (55.3%) were women. The mean (SD) length of hospital stay was 4.4 (4.6) days (median, 3.0 days). Of the eligible patients, 32 549 were assessed as low-risk for VTE, whereas 1804 were at high risk with a contraindication for pharmacologic prophylaxis and 10 422 were at high risk without a contraindication for pharmacologic prophylaxis.