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Hydrochlorothiazide and risk of melanoma subtypes

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Abstract

Background: Hydrochlorothiazide (HCTZ), a common diuretic known to be photosensitizing and previously associated with non-melanoma skin cancer, was recently reported to be associated with two melanoma subtypes, nodular and lentigo, among residents of Denmark. Our goal was to examine whether Danish findings could be replicated in a US cohort, using a similar study design and analysis.

Methods: Among non-Hispanic White enrollees of Kaiser Permanente Northern California, we conducted an analysis of 9176 melanoma cases and 264 781 controls, matched on age, sex and time in health plan. We examined use of HCTZ prior to cancer diagnosis (cases) or comparable date for controls, categorized as never use, ever use and high use (≥50 000 mg). Electronic health records provided data on prescriptions, cancer diagnoses, and covariates. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for education, income and number of dermatology, internal medicine and urgent care visits.

Results: We observed a small increase in risk of melanoma, all types combined, associated with high use (≥50 000 mg) of HCTZ (OR = 1.11, 95% CI 1.00–1.23) and no evidence of a dose–response. Risk was more elevated for lentigo subtype (OR = 1.57, 95% CI 1.01–2.42). The somewhat elevated risk for nodular subtype was not statistically significant (OR = 1.22, 95% CI 0.78–1.90). There was very little association of high use with the superficial spreading subtype (OR = 1.05, 95% CI 0.80–1.37).

Conclusions: Our findings support a recent report of an association between high use of HCTZ and increased risk of the lentigo subtype of melanoma.

KEYWORDS
hydrochlorothiazide, melanoma

Although the literature is not entirely consistent, we and others have reported markedly elevated risks of cutaneous squamous cell carcinoma (cSCC) among high users of hydrochlorothiazide (HCTZ).[1–7] This is biologically plausible, since HCTZ is photosensitizing[8] and cSCC is strongly associated with cumulative sun exposure.[9]

Sun exposure is also a risk factor for melanoma, although the relation is complex, with some subtypes more strongly associated with cumulative sun exposure in adulthood and later age at onset.[10,11] Thus, use of HCTZ may increase the risk of melanoma, particularly of subtypes most strongly related to sun exposure in mid- or late life, when treatment of hypertension is also common.

Using health data from national Danish registries, we previously observed an increased risk of two melanoma subtypes, nodular and lentigo, among high users of HCTZ.[12] In this study, we examined whether Danish findings could be replicated in a US cohort, using a similar study design and analysis.

1 | METHODS

The study was conducted within Kaiser Permanente Northern California (KPNC), an integrated healthcare system providing comprehensive services to over 4 million enrollees. Electronic health records include data on all prescriptions dispensed from KPNC pharmacies since 1996, a high-quality cancer registry with complete coverage since 1988, diagnoses and procedures associated with inpatient and outpatient encounters since 1996, and demographic information from US Census Bureau data (see reference 13 for description of Census block).

Our study cohort included enrollees to KPNC between January 1, 1996, and June 30, 2014, with pharmacy benefits. We excluded human immunodeficiency virus (HIV)-positive individuals and those with prior registry-recorded cancer. For each case, we selected up to 50 cancer-free controls, matched for birth year (exact year), sex, and year of joining KPNC (exact year). For cases, the index date was diagnosis; for controls, the index date was the date providing equal follow-back time to their matched case. This matching and selection of index date resulted in identical ages, sex, and calendar time of follow-up for case–control sets. For this study, we restricted the cases and controls to non-Hispanic Whites, since they are at highest melanoma risk. We used the cancer registry, which captures information from pathology reports and other medical records, to identify 9176 individuals with an invasive melanoma (cases); stages were localized ($n = 8076$), regional ($n = 638$), distant ($n = 255$), and unspecified ($n = 207$). Histologic diagnoses were: superficial spreading ($n = 2241$), nodular ($n = 477$), lentigo ($n = 377$), 10 other substantially less common subtypes (total $n = 572$) and a large number of unspecified ($n = 5509$).

HCTZ use was ascertained from cohort entry to 2 years before index date and was based on prescriptions filled at KPNC pharmacies. Cumulative dose was calculated by multiplying pill strength by number of pills for each prescription and then adding across all prescriptions. We assumed all pills were consumed. We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). These models retain matched sets of cases and controls and therefore control for potential confounding by matching factors (i.e., age, sex, calendar time). Model 1 did not include covariates. Model 2 included education and income level (from US Census block of residence)[13] and number of dermatology, internal medicine and urgent care visits, from cohort entry to 1 year before index date. Institutional review board approval was obtained; written informed consent was waived.

2 | RESULTS

Over 70% of both cases and controls were aged 50 years or older and both groups were slightly more male than female (Table 1). Cases and controls had similar education with almost 90% living in a Census block in which 50% or more had at least some college education. Cases were slightly more likely than controls to have one or more dermatology visits but cases and controls had similar number of internal medicine and urgent care visits.

Approximately 20% of cases and controls were ever users of HCTZ; approximately 5% were high users (≥ 50 000 mg) (Table 2). We observed only a very modest increased risk of melanoma, all subtypes combined, associated with high use of HCTZ (OR = 1.11, 95% CI 1.0–1.23, model 2) and no evidence of a dose–response. However, associations with high use were stronger for nodular (OR = 1.22, 95% CI 0.78–1.90, model 2) and lentigo (OR = 1.57, 95% CI 1.01–2.42, model 2) subtypes and there was a suggestion that risk increased with increasing dose, although risk dropped with the very high use (≥100 000 mg), which may be due to small numbers. In contrast, there was little association between HCTZ use and risk of the superficial spreading subtype.

Overall and subtype-specific ORs were generally similar in sensitivity analyses restricted to individuals with a diagnosis of hypertension, although ORs for nodular subtype were attenuated. For high use, OR = 1.05, 95% CI 0.94–1.18 for all subtypes combined; OR = 1.03, 95% CI 0.77–1.36 for superficial spreading; OR = 1.04, 95% CI 0.66–1.65 for nodular; and OR = 1.57, 95% CI 0.99–2.50 for lentigo). In sensitivity analyses examining different potential induction/latency periods and potential protopathic bias, we observed similar ORs when we used a lag (period when prescriptions are ignored) of 1, 2 or 3 years prior to diagnosis or index date in controls (not shown). We also conducted subgroup analyses to explore potential differences in risk by age, but only the most common subtype, superficial spreading, had sufficient numbers of cases. In these analyses, the OR for high use of HCTZ was 3.16 (95% CI 1.09–9.19) among individual less than 50 years (based on only 4 exposed cases), 0.75 (95% CI 0.45–1.24) among those 50–69 years, and 1.15 (95% CI 0.82–1.63) among those 70 years and older. We did not see any differences in the association of HCTZ use and melanoma risk by sex, either overall or for the superficial spreading subtype.

3 | DISCUSSION

To our knowledge, this is the second study to report on the association between HCTZ use, including cumulative dose, and risk of melanoma stratified by histologic subtype. Our subtype findings are consistent with their etiology. Lentigo melanoma usually occurs on chronically sun-exposed skin and is associated with presence of actinic keratosis and solar lentigines,[10] which is similar to cSCC.[9] In addition, lentigo melanoma has a later onset and is the most frequent subtype over age 60 years,[11] when treatment for hypertension is also common. While nodular melanoma has an earlier onset, it also peaks after age 60. In contrast, superficial spreading melanoma is the most common subtype between ages 30 and 60 and is less likely than lentigo subtype to occur on parts of the body chronically exposed to the sun.[11]

Our findings suggesting an increased risk of lentigo and nodular subtypes are generally consistent with results from our recently published study conducted within the Danish population.[12] In that study of 19 273 cases and 192 739 controls, the associations with high use

TABLE 1 Patient characteristics of invasive melanoma cases ($n = 9176$) and controls ($n = 264\,781$)

	Cases		Controls	
Characteristic	***n***	**%**	***n***	**%**
Age at index date[a]				
<30 years	304	(3.3)	5688	(2.2)
30–39	660	(7.2)	12 746	(4.8)
40–49	1350	(14.7)	31 877	(12.0)
50–59	2062	(22.5)	57 362	(21.7)
60–69	2099	(22.9)	65 689	(24.8)
70+	2701	(29.4)	91 419	(34.5)
Sex[a]				
Male	5195	(56.6)	152 012	(57.4)
Female	3981	(43.4)	112 769	(42.6)
Percent with some high school or less[b]				
<10%	7852	(85.6)	220 501	(83.3)
10%–19%	909	(9.9)	30 248	(11.4)
20+ %	339	(3.7)	11 291	(4.3)
Unknown	76	(0.8)	2741	(1.0)
Percent with at least some college[b]				
<25%	63	(0.7)	2826	(1.1)
25%–49%	957	(10.4)	33 489	(12.7)
50+ %	8080	(88.1)	225 725	(85.2)
Unknown	76	(0.8)	2741	(1.0)
Median annual household income[b]				
<$50 000	1473	(16.0)	46 571	(17.6)
$50 000–99 999	4941	(53.9)	145 197	(54.8)
$100 000 +	2685	(29.3)	70 263	(26.5)
Unknown	77	(0.8)	2750	(1.0)
Number of dermatology visits[c]				
0	4309	(47.0)	146 306	(55.3)
1–4	2533	(27.6)	74 908	(28.3)
5–9	1070	(11.7)	23 501	(8.9)
10+	1264	(13.8)	20 066	(7.6)
Number of internal medicine visits[c]				
0	1540	(16.8)	41 659	(15.7)
1–9	2950	(32.1)	79 764	(30.1)
10–29	2773	(30.2)	82 785	(31.3)
30+	1913	(20.8)	60 573	(22.9)
Number of urgent care visits[c]				
0	6819	(74.3)	192 590	(72.7)
1–4	2027	(22.1)	62 574	(23.6)
5+	330	(3.6)	9617	(3.6)

[a]Matching factors (we matched on birth year and date of diagnosis/index date, resulting in identical ages for cases and matched controls). Note, age and sex distributions for cases and controls are not identical because of restriction to non-Hispanic whites after matching occurred, which also resulted in fewer than 50 controls for most cases.

[b]From the US Census block of residence on the index date for education and median annual household income.

[c]For the period from start of follow-up to 1 year prior to the index date.

TABLE 2 Association between exposure to hydrochlorothiazide and risk of invasive melanoma, overall and by histologic subtype

	Cases	Controls	Adjusted OR – Model 1[a] (95% CI)	Adjusted OR – Model 2[b] (95% CI)
Overall	(*n* = 9176)	(*n* = 264 781)		
Non-use	7336	208 447	1.0 (ref.)	1.0 (ref.)
Ever use	1840	56 334	1.06 (1.00–1.12)	1.09 (1.03–1.16)
High-use (≥50 000 mg)	450	13 754	1.08 (0.98–1.20)	1.11 (1.00–1.23)
Cumulative dose				
1–24 999 mg	988	31 438	1.01 (0.94–1.09)	1.04 (0.97–1.12)
25 000–49 999 mg	402	11 142	1.18 (1.06–1.31)	1.21 (1.08–1.35)
50 000–99 999 mg	314	9489	1.10 (0.98–1.24)	1.13 (1.00–1.28)
≥100 000 mg	136	4265	1.06 (0.89–1.27)	1.06 (0.89–1.27)
Superficial spreading	(*n* = 2241)	(*n* = 63 396)		
Non-use	1896	53 095	1.0 (ref.)	1.0 (ref.)
Ever use	345	10 301	1.09 (0.95–1.24)	1.15 (1.00–1.31)
High-use (≥50 000 mg)	66	2212	0.99 (0.76–1.29)	1.05 (0.80–1.37)
Cumulative dose				
1–24 999 mg	200	6077	1.05 (0.90–1.23)	1.11 (0.95–1.30)
25 000–49 999 mg	79	2012	1.30 (1.02–1.65)	1.36 (1.07–1.74)
50 000–99 999 mg	43	1581	0.91 (0.66–1.25)	0.97 (0.71–1.34)
≥100 000 mg	23	631	1.22 (0.79–1.88)	1.26 (0.81–1.95)
Nodular	(*n* = 477)	(*n* = 14 322)		
Non-use	365	10 957	1.0 (ref.)	1.0 (ref.)
Ever use	112	3365	1.13 (0.89–1.44)	1.21 (0.95–1.56)
High-use (≥50 000 mg)	25	759	1.15 (0.74–1.78)	1.22 (0.78–1.90)
Cumulative dose				
1–24 999 mg	63	1934	1.10 (0.83–1.47)	1.19 (0.89–1.59)
25 000–49 999 mg	24	672	1.19 (0.77–1.84)	1.28 (0.82–1.99)
50 000–99 999 mg	22	551	1.38 (0.87–2.19)	1.47 (0.92–2.34)
≥100 000 mg	3	208	0.50 (0.15–1.59)	0.52 (0.16–1.67)
Lentigo	(*n* = 377)	(*n* = 12 352)		
Non-use	283	9364	1.0 (ref.)	1.0 (ref.)
Ever use	94	2988	1.11 (0.85–1.45)	1.17 (0.89–1.54)
High-use (≥50 000 mg)	30	710	1.55 (1.01–2.38)	1.57 (1.01–2.42)
Cumulative dose				
1–24 999 mg	45	1677	0.95 (0.68–1.32)	1.01 (0.72–1.43)
25 000–49 999 mg	19	601	1.14 (0.70–1.87)	1.22 (0.74–2.01)
50 000–99 999 mg	23	510	1.66 (1.04–2.65)	1.70 (1.05–2.75)
≥100 000 mg	7	200	1.29 (0.58–2.86)	1.25 (0.56–2.80)

[a]Adjusted for age, sex, and calendar time (by use of risk-set matching and conditional logistic analysis). NHW only.
[b]Fully adjusted model, that is, additionally adjusted for highest education achieved and socioeconomic level based on the US Census block of residence, and number of ambulatory visits, including dermatology visits (0, 1–4, 5–9, 10+), internal medicine visits (0, 1–9, 10–29, 30+), and urgent care visits (0, 1–4, 5+) for the period from start of follow-up to 1 year prior to the index date.

were slightly stronger, with OR = 1.22 (95% CI 1.09–1.36) for melanoma, all subtypes combined; OR = 2.05 (95% CI 1.54–2.72) for nodular; and OR = 1.61 (95% CI 1.03–2.50) for lentigo. As in our study, superficial spreading subtype was not associated with high use of HCTZ in the Danish study (OR = 1.11, 95% CI 0.97–1.27). However, in both studies there was some evidence of an elevated risk of superficial spreading among younger adults. In unpublished results from the Danish study (personal communication from co-author Pottegård), the OR for high use of HCTZ was 1.52 (95% CI 0.68–3.44) for adults under 50 years, 1.42 (95% CI 0.98–2.07) for adults 50–60 years, 1.10 (95% CI 0.91–1.33) for adults 60–74 years, and 1.0 (0.78–1.28) for those 75 years and older.

Three other Danish studies, one Swedish, two UK studies and one multi-country European study examined melanoma risk (all subtypes combined) and use of thiazides[3,6,7,14–18]; ORs for any use were between 1.1 and 1.4 and borderline or not statistically significant. None of the three studies examining dose response observed a clear increase in risk with increasing duration of use.[6,11,12] A US study observed a more elevated OR for any use of thiazides and risk of all melanoma subtypes combined (OR = 1.82, 95% CI 1.01–3.82); however, this association disappeared when cases were restricted to those diagnosed at least 12 months after thiazide use.[19]

The strengths of our study include the high-quality prescription and cancer data—and a large and stable population receiving comprehensive care within a system with an integrated medical record. We used a study design that was very similar to the Danish study, which optimizes comparability of findings. Given the lack of association with other anti-hypertensive medications in the Danish study, we only examined HCTZ. As with the Danish study, we did not have information on some important risk factors for melanoma, including sun exposure, history of sunburns, skin tone and tendency to burn, or family history of melanoma. Thus, our results may be subject to confounding. However, given HCTZ's known photosensitizing properties, its use might be less common among individuals at higher risk of sunburn (e.g., fair skin, high sun exposure) and those taking HCTZ may be more likely to use sunscreen or stay out of the sun; these behaviors would attenuate associations between HCTZ use and melanoma risk. The cases did not undergo a standardized pathology review and a large proportion had unspecified subtype in the cancer registry. However, the characteristics of cases with and without specified subtype were quite similar, as were the associations of risk with HCTZ use, suggesting these two groups of cases were not substantially different.

4 | CONCLUSIONS

The results of this study, together with findings from our recent Danish study, suggest that high use of HCTZ is associated with an elevated risk of melanoma but only for the lentigo, and possibly nodular, subtypes. Risk may also be elevated for superficial spreading subtype among younger adults. The etiology of cutaneous melanoma appears to vary by histologic subtype, with some more strongly associated with cumulative sun exposure and later onset.[10,11] Thus, future studies of melanoma subtypes should be conducted to confirm our findings. Given the widespread use of HCTZ, even a modest increase in melanoma risk would have substantial public health significance.

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CONFLICT OF INTEREST

Dr Habel and Ms. Achacoso had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr 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. Other authors have no potential conflicts of interests.

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