

Risk of squamous cell carcinoma of the lip and cutaneous melanoma in older Australians using hydrochlorothiazide: A population-based case-control study

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Funding information

This work was supported by the Australian Government Department of Health, the NHMRC Centre of Research Excellence in Medicines and Ageing (CREMA; ID: 1060407), and a Cooperative Research Centre Project (CRC-P) Grant from the Australian Government Department of Industry, Innovation and Science (ID: CRC-P-439). CMV and HZ are supported by UNSW Scientia Fellowships. The funders of the study had no role in the data analysis, interpretation or drafting of the final manuscript.

Abstract

Recent European and US studies reported increased risks of skin cancers associated with hydrochlorothiazide (HCTZ) treatment. Our study aimed to determine the risk of lip cancer and malignant melanoma among Australians prescribed HCTZ. We conducted a case-control study nested within a population of veterans residing in New South Wales in 2004–2015, using Australian Department of Veterans' Affairs data linked with cancer registrations, hospitalisation and prescription dispensings. Among DVA healthcare card holders 65 years and older, we identified incident cases of squamous cell carcinoma of the lip and of cutaneous melanoma, each matched with up to 20 controls through risk-set sampling. We estimated odds ratios (ORs) associating HCTZ use with each cancer using conditional logistic regression, adjusting for predefined confounders. For lip cancer (45 cases), ever-use of HCTZ yielded an OR of 2.6 (95% CI: 1.4–5.0) and high HCTZ use (≥ 25 000 mg) an OR of 4.7 (95% CI: 1.6–13.7). For cutaneous melanoma (659 cases), ever-use of HCTZ resulted in an OR of 1.2 (95% CI 1.0–1.5) and high HCTZ use in an OR of 1.2 (95% CI: 0.8–1.8). Our findings align with risk estimates from previous studies and provide further evidence that HCTZ's photosensitising properties may promote carcinogenesis in sun-exposed tissues.

KEYWORDS

Australia, hydrochlorothiazide, lip cancer, malignant melanoma, skin cancer

1 | INTRODUCTION AND BACKGROUND

Hydrochlorothiazide (HCTZ) is a thiazide diuretic indicated as first-line treatment for hypertension,^{1,2} often prescribed in combination with other antihypertensive medicines. Given the high prevalence of hypertension and guidelines recommending thiazide diuretics to treat the condition, HCTZ is one of the most widely used medicines, globally^{1,3-5} as well as in Australia.⁶

Thiazide diuretics are known to possess photosensitising properties⁷; in 2013, the International Agency for Research on Cancer classified HCTZ as “possibly carcinogenic to humans” (Group 2B).⁸ Recent studies reported HCTZ increased the risk of developing a range of skin cancers, particularly squamous cell carcinomas (SCCs),^{2,7,9-13} and warnings from medicines regulatory agencies in Europe,¹⁴ the UK,¹⁵ Canada,¹⁶ Singapore¹⁷ and New Zealand¹⁸ followed from October 2018. These findings and regulatory warnings are particularly relevant for Australia, which has the highest incidence of skin cancer in the world.¹⁹

Despite the elevated baseline risk and widespread use of HCTZ among Australians, little is known about the association between HCTZ and risk of developing skin cancer in Australia. Therefore, we sought to examine the association between the use of HCTZ and risk of SCC of the lip (lip cancer) and cutaneous melanoma (malignant melanoma) in a population-based cohort of older Australians.

2 | MATERIALS AND METHODS

2.1 | Study setting and data sources

Australia maintains a universal healthcare system for Australian citizens and permanent residents. In addition, the Australian Government Department of Veterans’ Affairs (DVA) funds the healthcare and pharmaceutical items for eligible veterans, war widows/ widowers and their dependents.²⁰

We used the DVA client database linked with the New South Wales Cancer Registry (NSWCR), the Repatriation Pharmaceutical Benefits Scheme (RPBS) dispensing data and the New South Wales (NSW) admitted patients data collection (APDC).²⁰ The RPBS provides access to all pharmaceutical items available to the general community under the Pharmaceutical Benefits Scheme (PBS), as well as additional medicines available only to DVA healthcare card holders.²¹ The PBS is a national programme that provides subsidised access to approved medicines for all Australians. The DVA client database contains information for all Australians eligible for DVA-funded benefits, including residential history. The NSWCR includes information about all notifiable primary malignant cancers diagnosed in NSW, the most populous

state of Australia. Cutaneous basal cell carcinomas and SCC are not notifiable diagnoses in NSW—with the exceptions of SCC of the skin of anus, vulva, penis, scrotum and vermilion surface, and border of the lip—and do not appear in NSWCR data. We chose to examine SCC of the lip as previous studies have also examined this cancer^{10,12,13} and because it is the only cutaneous SCC diagnosis that appears in sufficient numbers in our data set. The NSWCR receives information from pathology laboratories, public and private hospitals, radiotherapy and medical oncology departments, aged care facilities, day procedure centres and the NSW Registry of Births, Deaths and Marriages.²² The NSW APDC contains data for all inpatient hospital separations and emergency department visits.²⁰ The time period observed in the data is January 2004 through December 2015, while the NSWCR contains cancer notifications from January 1972 through December 2015.

2.2 | Study design and analysis

We performed a nested case-control analysis comparing HCTZ use in DVA healthcare card holders diagnosed with lip cancer or malignant melanoma with HCTZ use in those without either diagnosis. To facilitate interpretability and comparability, we directly aligned our study design and statistical analyses to recently published studies.^{11,12}

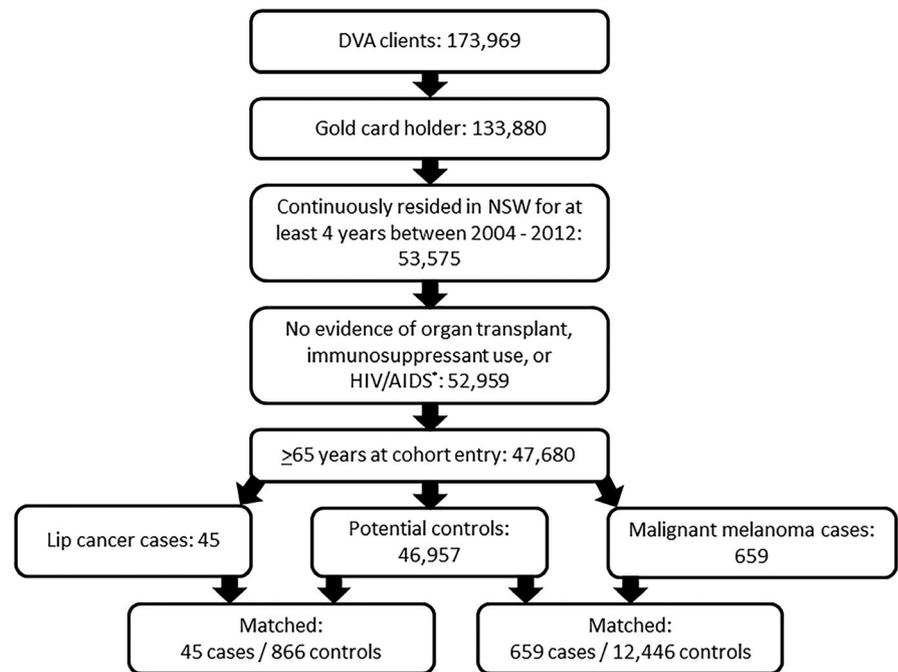
2.2.1 | Study participants

We included all DVA clients holding a DVA Gold Card (entitled to clinically required healthcare treatment for all conditions) as these clients are able to access prescribed medicines with a reduced co-payment amount, meaning all of their dispensed medicines are captured in our dispensing data from the time their Gold Card benefits began.²⁰ For clients whose Gold Card benefits began prior to 1 January 2004, the date on which our dispensing records began, we considered 1 January 2004 as the Gold Card start date. We excluded clients with evidence of organ transplant, HIV/AIDS diagnosis or use of immunosuppressants. As the Gold Card holding population is predominantly over 65 years of age,²⁰ we included only those aged 65 years or older at the time their Gold Card benefits began (Figure 1).

2.2.2 | Case and control selection

We defined cases as those Gold Card holders with a histologically confirmed diagnosis of lip cancer or invasive malignant melanoma between January 2008 and December 2015, and no history of any notifiable cancer prior to either diagnosis (the index date). As we are only able to capture cancer diagnoses for clients residing in NSW, we further required cases

FIGURE 1 Flow chart of case and control selection



to continuously reside in NSW for at least 4 years prior to the index date. We used risk-set sampling to match up to 20 controls for each lip cancer and malignant melanoma case,²³ applying the same residency restrictions as for cases. We matched controls to cases on age at the time Gold Card benefits began and sex, and we allowed cases to act as controls prior to becoming cases. The observed odds ratios (ORs) therefore provide estimates of the incidence rate ratios (IRR) expected from a cohort study in the source population.²⁴

2.2.3 | HCTZ use

We considered a dispensing record for HCTZ—as a single agent or in combination with other medicines—prior to the index date as indicating ever-use of HCTZ (see Table S1 for a complete list of the relevant ATC codes). We did not include HCTZ dispensings within 12 months prior to the index date to allow for an induction period and to mitigate the potential for increased contact with health professionals prior to cancer diagnosis leading to increased HCTZ prescribing, thus creating spurious associations.²⁵ To explore a dose-response relationship between HCTZ use and skin cancer risk,¹² we calculated the cumulative amount of HCTZ, in mg, dispensed to Gold card holders up to 12 months prior to the index date. Consistent with existing studies, we considered $\geq 25\,000$ mg as high exposure to HCTZ.¹²

2.2.4 | Additional variables

To control for potential confounding, we ascertained use of additional medicines potentially related to skin cancer risk. These

included medicines with known photosensitising properties including oral and topical retinoids, macrolides, tetracycline, aminoquinolines and amiodarone; as well as medicines with possible anticancer properties including prescription strength aspirin, non-steroidal anti-inflammatories (NSAIDs) and statins.^{12,26} We defined use of these potential confounding medicines as at least two dispensings on different dates prior to the index date and excluded any dispensings occurring in the 12 months prior to the index date.¹² We further ascertained comorbidity burdens using the Charlson comorbidity index applied to hospitalisation records,²⁷ again excluding records occurring within 12 months of the index date. Finally, we derived a measure of ambient ultraviolet radiation (UVR) exposure based on the location of the Gold Card holders' residences—at the level of the Australian Bureau of Statistics' Statistical Local Area (SLA)²⁸—at the start of Gold Card benefits. We created three groups based on tertiles of latitude within NSW and where SLAs fell within those tertiles: North (highest UVR exposure), Central (includes Sydney; middle UVR exposure) and South (lowest UVR exposure; Figure S1).

2.2.5 | Statistical analysis

We used conditional logistic regression to calculate crude and adjusted ORs and 95% confidence intervals (95% CI) to compare HCTZ exposure in Gold Card holders diagnosed with lip cancer or malignant melanoma and matched cancer-free controls. As cases and controls were already matched on age at Gold Card start and sex, and as we used conditional regression, we did not include age and sex in our adjusted models. For malignant melanoma, we performed further analyses stratifying

	Lip cancer		Malignant melanoma	
	Cases (n = 45)	Controls (n = 866)	Cases (n = 659)	Controls (n = 12 446)
Age at cohort entry, median (IQR)	79 (75-81)	79 (75-81)	81 (78-83)	81 (78-83)
Males, n (%)	25 (56)	500 (58)	443 (67)	8,399 (67)
HCTZ use, n (%)				
Never-use	27 (60)	687 (79)	502 (76)	9,976 (80)
Ever-use	18 (40)	179 (21)	157 (24)	2,470 (20)
Cumulative HCTZ amount, n (%)				
1-4999 mg	^a	^a	46 (7)	670 (5)
5000-9999 mg	^a	^a	23 (3)	496 (4)
10 000-24 999 mg	^a	^a	58 (9)	889 (7)
≥25 000 mg	6 (13)	30 (3)	30 (5)	415 (3)
Ever-use of other medicines, n (%)				
Photosensitising medicines	11 (24)	154 (18)	123 (19)	2293 (18)
Aspirin	^a	^a	20 (3)	432 (3)
NSAIDs	20 (44)	354 (41)	273 (41)	4794 (39)
Statins	22 (49)	473 (55)	367 (56)	6696 (54)
Charlson comorbidity index, n (%)				
No comorbidities	30 (67)	529 (61)	442 (67)	7559 (61)
1-2 comorbidities	^a	^a	149 (23)	2808 (23)
≥3 comorbidities	^a	^a	68 (10)	2079 (17)
UVR group, n (%)				
South, lowest	^a	^a	63 (10)	1,796 (14)
Central, middle	37 (82)	627 (72)	489 (74)	8929 (72)
North, highest	^a	^a	107 (16)	1721 (14)
Use of other antihypertensive medicines, n (%)				
Furosemide	17 (38)	315 (36)	204 (31)	4579 (31)
ACE inhibitors	21 (47)	419 (48)	315 (48)	5680 (46)
ATII agonists	10 (22)	139 (16)	203 (31)	3814 (31)
Calcium channel blockers	14 (31)	198 (23)	246 (37)	4579 (37)
Indapamide	^a	^a	43 (7)	665 (5)

Note: © Commonwealth of Australia 2020.

Abbreviations: HCTZ, hydrochlorothiazide; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; and UV, ultraviolet.

^aCell counts less than 5 cannot be reported due to ethical restrictions. Where categories are mutually exclusive, multiple cells have been suppressed to prevent implicitly reporting those less than 5.

TABLE 1 Characteristics of lip cancer and malignant melanoma cases and controls

the disease by histological subtype—superficial spreading melanoma, nodular melanoma and lentigo melanoma.

2.2.6 | Secondary analyses

To assess the role of potential confounding by indication, we repeated the main analysis for other diuretics and

antihypertensive medicines with similar indications to HCTZ (ie mild to moderate hypertension). These medicines included furosemide, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II (ATII) antagonists, calcium channel blockers (CCBs) and indapamide. Exposure to each medicine was ascertained as for ever-use of HCTZ, described above. We included ever-use of HCTZ as a covariate in each of the models for these secondary analyses.

We performed all analyses in SAS version 9.4 (SAS Institute) and R version 3.6.

2.3 | Ethics approval, data access and consent to participate

Our study was approved by the NSW Population and Health Services Research Ethics Committee (approval number: 2013/11/494) and the Departments of Defence and Veterans' Affairs Human Research Ethics Committee (approval number: E013/015). These Committees granted a waiver of consent in line with the National Statement on Ethical Conduct in Human Research (2007; Chapter 2.3) and the Guidelines approved under Section 95/95A of the Privacy Act 1988.

3 | RESULTS

We identified 45 lip cancer cases and 659 malignant melanoma cases, matched to 866 and 12 446 controls, respectively (Figure 1). Lip cancer cases and controls had similar characteristics though a larger proportion of cases resided in the

central latitudes of NSW (Figure S1); malignant melanoma cases and controls were similar across all available characteristics (Table 1).

HCTZ was most commonly dispensed in combination with ATII antagonists (77% and 80% for lip cancer and malignant melanoma controls, respectively), ACE inhibitors (16%, 14%) and amiloride (4%, 3%). HCTZ was dispensed to 40% and 24% of lip cancer and malignant melanoma cases, respectively, and to 21% and 20% of their respective controls. The resulting adjusted OR was 2.6 (95% CI: 1.4-5.0) for lip cancer and 1.2 (95% CI: 1.0-1.5) for malignant melanoma (Table 2). High use of HCTZ was observed in 13% of lip cancer cases (3% of controls) and 5% of malignant melanoma cases (3% of controls), resulting in adjusted ORs of 4.7 (95% CI: 1.6-13.7) for lip cancer and 1.2 (95% CI: 0.8-1.8) for malignant melanoma (Table 2). When stratifying by histological subtype, we observed elevated ORs for superficial spreading melanoma (OR: 1.6; 95% CI: 1.2-2.2) with ever-use and for lentigo melanoma (OR: 2.1; 95% CI: 1.0-4.5) with high use of HCTZ (Table 3). We found no association with nodular melanoma.

We did not observe associations between either cancer type and ever-use of ACE inhibitors, ATII antagonists, CCBs

TABLE 2 Association between exposure to hydrochlorothiazide and risk of lip cancer and malignant melanoma, according to cumulative amount of hydrochlorothiazide use

	Cases	Controls	Crude OR	95% CI	Adjusted OR	95% CI
Lip cancer lip cancer						
Never used	27	687	1.00	Reference	1.00	Reference
Ever used	18	179	2.61	1.39-4.89	2.62	1.37-4.99
High use (>25 000 mg)	6	30	4.88	1.78-13.38	4.69	1.61-13.66
Cumulative amount (mg)						
1-4999	^a	^a	1.48	0.43-5.07	1.58	0.45-5.50
5000-9999	^a	^a	4.11	1.49-11.31	4.00	1.41-11.33
10 000-24 999	^a	^a	1.68	0.57-4.97	1.69	0.55-5.13
>25 000	6	30	4.88	1.78-13.38	4.69	1.61-13.66
Malignant melanoma						
Never used	502	9,976	1.00	Reference	1.00	Reference
Ever used	157	2,470	1.22	1.01-1.47	1.22	1.01-1.46
High use (>25 000 mg)	30	415	1.26	0.85-1.87	1.22	0.82-1.80
Cumulative amount (mg)						
1-4999	46	670	1.31	0.96-1.79	1.33	0.97-1.83
5000-9999	23	496	0.91	0.60-1.40	0.93	0.61-1.42
10 000-24 999	58	889	1.30	0.98-1.72	1.28	0.97-1.70
>25 000	30	415	1.26	0.85-1.87	1.22	0.82-1.80

Note: © Commonwealth of Australia 2020.

Abbreviations: CI, confidence interval; OR, odds ratio.

^aCell counts less than 5 cannot be reported due to ethical restrictions. Where categories are mutually exclusive, multiple cells have been suppressed to prevent implicitly reporting those less than 5.

	Cases	Controls	Crude OR	95% CI	Adjusted OR	95% CI
Superficial spreading melanoma						
Never used	141	3374	1.00	Reference	1.00	Reference
Ever used	58	823	1.60	1.16-2.20	1.60	1.16-2.21
High use (≥25 000 mg)	8	140	1.18	0.56-2.50	1.10	0.52-2.36
Nodular melanoma						
Never used	108	2421	1.00	Reference	1.00	Reference
Ever used	29	629	0.97	0.63-1.48	0.95	0.62-1.46
High use (≥25 000 mg)	7	105	1.26	0.85-1.87	1.14	0.50-2.61
Lentigo melanoma						
Never used	103	2437	1.00	Reference	1.00	Reference
Ever used	31	607	1.20	0.79-1.81	1.18	0.78-1.79
High use (≥25 000 mg)	9	94	2.17	1.04-4.52	2.13	1.02-4.47

Note: ©Commonwealth of Australia 2020.

Abbreviations: CI, confidence interval; OR, odds ratio.

or indapamide; however, ever-use of furosemide was associated with a marginally reduced risk of malignant melanoma in the adjusted model (OR: 0.8; 95% CI: 0.7-1.0) (Table S2).

4 | DISCUSSION

In this population-based study nested within Australia's most populous state, we found elevated risks of both lip cancer and malignant melanoma associated with HCTZ use. Our findings are in line with those reported from Denmark,^{11,12} the UK,¹⁰ and the United States,¹³ and further support the existence of an association between HCTZ use and increased risks of skin cancer. This association is particularly relevant in Australia, as it is home to the highest incidence of skin cancer in the world and the use of HCTZ is widespread.

We observed a twofold increase in the risk of lip cancer associated with ever-use of HCTZ, similar to risks reported from Denmark (OR: 2.1; 95% CI: 1.7-2.6),¹² the UK (IRR: 2.9; 95% CI: 1.3-6.2),¹⁰ and the United States (OR: 2.2; 95% CI: 1.7-2.8).¹³ Two of these studies also noted an increased risk of lip cancer associated with higher use of HCTZ.^{12,13} The time period covered by our data did not allow us to replicate the exact cumulative use groupings of these previous studies—and with just 45 lip cancer cases in total, our study was not powered to explore risk by cumulative exposure with a high degree of precision—but our point estimate for ≥25 000 mg of HCTZ use (equivalent to approximately 3 years' worth of HCTZ use; OR: 4.7; 95% CI: 1.6-13.7) was within the 95% CIs of both the “high use (≥25 000 mg)”

TABLE 3 Association between exposure to hydrochlorothiazide and risk of malignant melanoma, according to ever-use and high use of hydrochlorothiazide and melanoma subtype

group reported in Denmark (OR: 3.9; 95% CI: 3.0-4.9)¹² and the “≥5-year supply” group reported from the United States (OR: 4.2; 95% CI: 2.8-6.3).¹³ Our finding is also in line with recent studies that have found increased risks of non-lip SCC associated with the use of HCTZ and other thiazides,^{7,29,30} suggesting that the increased risk we observed may apply to SCC in general.

While we observed a marginally increased risk of malignant melanoma associated with HCTZ use, our estimate was within previous estimates from Denmark (IRR: 1.32, OR: 1.16).^{7,11} Like these earlier studies, we too did not observe increased risk associated with larger cumulative exposures to HCTZ. When stratifying by histological subtype, we observed elevated point estimates for superficial spreading melanoma with ever-use of HCTZ and for lentigo melanoma with high use of HCTZ, but no association for nodular melanoma. This aligns with estimates reported from Denmark for superficial spreading and lentigo melanoma, as they reported an OR of 1.6 (95% CI 1.3-2.0) for lentigo melanoma. However, our findings do not support the previously reported estimate for nodular melanoma (OR: 2.1; 95% CI: 1.5-2.7).¹¹ Of note, the finding of an increased risk specific to lentigo melanoma aligns with our understanding that lentigo melanoma is the subtype most dependent on adulthood UV radiation.³¹ More research into the association of HCTZ use and malignant melanoma subtypes appears justified. It would also be informative to examine in situ cutaneous melanoma.

To explore the role of confounding by indication—that the elevated risks of lip cancer and malignant melanoma were related to patients' underlying hypertension rather

than HCTZ use—we further explored the risks of lip cancer and malignant melanoma associated with several medicines having similar indications to HCTZ—furosemide, ACE inhibitors, ATII antagonists, CCBs and indapamide. We found no associations between any of these medicines and lip cancer; however, we observed a marginally protective association between furosemide use and malignant melanoma (OR: 0.8, 95% CI: 0.7-1.0). Our estimate is similar to those from previous studies reporting null effects,^{7,32} suggesting the association we observed may be spurious.

Hypertension is one of the most prevalent health conditions in Australia³³ and the world,³⁴ and thiazide diuretics are a useful and effective treatment for patients with hypertension. They also are occasionally useful in other conditions, such as congestive heart failure. In response to the recent studies we replicated here, national and supra-national medicines regulatory bodies have begun to issue warnings to prescribers about the risks of HCTZ use and skin cancer.¹⁴⁻¹⁸ Discontinuing or switching treatment to other agents might lead to a range of other adverse consequences: adverse drug effects, decreased adherence and/or poorer blood pressure control. In Australia, HCTZ is most often prescribed as a component in a fixed-dose combination with one or more of 14 other agents (97% of HCTZ dispensings in our data), and switching to a similar combination with a different thiazide-like antihypertensive agent is not currently possible for any of these agents. SCCs are generally easily treated if detected early, but Australian prescribers should be aware of these potential skin cancer risks and consider if their patients should be advised to limit sun exposure or have more frequent skin checks.

Our study has several strengths and limitations. We used data from a large, population-based collection from Australia's most populous state, NSW. The people comprising these data sets have been shown to be representative of the wider Australian population of similar age.²⁰ Gold Card holders are, however, notably older than the Australian population at large,²⁰ and the median age of our study population was around 80 years. Our results cannot necessarily be generalised to a younger population, and further research in Australians <65 years is justified. We note that, while older, our study population had a small number of comorbidities, as ascertained through the Charlson comorbidity index, and they had never been diagnosed with cancer prior to the index diagnosis, suggesting considerable health resilience. Nevertheless, we observed significant relationships between HCTZ use and lip cancer and malignant melanoma. Most SCC diagnoses are not recorded in the NSWCR, and the only reportable SCC diagnosis for which we had sufficient numbers to examine was SCC of the lip. Still, we observed a small number of lip cancer cases, and while our risk estimates are similar to those reported in previous studies,^{10,12,13} our findings should be interpreted

with this limitation in mind. The cancer diagnosis data we used in our study go back as far as 1972, but our dispensing records began in 2004. Some people may have used HCTZ prior to 2004 and we did not observe that use. Likewise, our measures of cumulative use may be lower than the true values. A recent study from Taiwan found no associations between either lip cancer or melanoma and HCTZ use in the Taiwanese population, suggesting that HCTZ users with Caucasian skin type may be most at risk of developing these skin cancers.³⁵ We did not have data for skin type (or skin colour or ethnic background), but the majority of the Australian population is of European descent.³⁶ We also did not have data for smoking status (an important confounder for lip cancer); however, we note a recent UK study found that adjusting for smoking status did not alter the relationship between HCTZ use and lip cancer.¹⁰ A strength of our study is the incorporation of ambient UVR data. We ascertained UVR exposure based on residence at study entry, but did not have data on early-life or cumulative UVR exposure.³⁷ However, the risk estimates we observed for our UVR exposure groups suggested we were adjusting for relevant information (higher skin cancer risks in the North, lower risks in the South).

Our study provides further evidence that the photosensitising properties of HCTZ may promote SCC carcinogenesis, and possibly melanoma, in susceptible sun-exposed tissues. Our findings are the first from the Australian population—already at an elevated risk of developing skin cancer—and add to the growing body of data supporting the need for skin cancer prevention advice and behaviours, and potentially heightened surveillance, for individuals prescribed this important medication.

DISCLAIMER

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CONFLICT OF INTEREST

SP is a member of the Drug Utilisation Sub Committee of the Pharmaceutical Benefits Advisory Committee. The views expressed in this paper do not represent those of either Committee. AP has participated in research projects, unrelated to the present study, using grants provided by LEO Pharma to the institution where AP is employed. The remaining authors have no interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Daniels B, Pearson S-A, Vajdic CM, Pottg ard A, Buckley NA, Zoega H. Risk of squamous cell carcinoma of the lip and cutaneous melanoma in older Australians using hydrochlorothiazide: A population-based case-control study. *Basic Clin Pharmacol Toxicol.* 2020;00:1–9. <https://doi.org/10.1111/bcpt.13463>