# The Risk of Cutaneous Squamous Cell Carcinoma Among Patients with Type 2 Diabetes Receiving Hydrochlorothiazide: A Cohort Study

Jing de Haan-Du[1], Gijs W.D. Landman[1,2,3], Klaas H. Groenier[3], Pauline A.J. Vissers[4], Marieke W.J. Louwman[4], Nanne Kleefstra[3,5,6], and Geertruida H. de Bock[1]

## ABSTRACT

**Background:** Because of continuous hyperglycemia and hyperinsulinemia and the use of photosensitizing drug, hydrochlorothiazide (HCTZ), the risk of cutaneous squamous cell carcinoma (cSCC) might be increased among patients with diabetes. This study aimed to estimate the risk of cSCC among HCTZ users with type 2 diabetes, and to determine whether thiazide-like diuretics, another drug in the same class with HCTZ, would be safer.

**Methods:** We linked the benchmarking database in Dutch primary care, the Netherlands Cancer Registry, and the Dutch Personal Records Database (1998–2019). All 71,648 patients were included, except for those who had a history of skin cancer prior to cohort entry. We used Cox modeling to estimate the HRs and 95% confidence intervals for cSCC. The model was adjusted by cumulative exposure to each antihypertensive, age, sex, smoking, body mass index, blood pressure, serum creatinine, other confounding drug use at cohort entry, and cohort entry year.

**Results:** There were 1,409 cSCC events (23 among thiazide-like diuretics users), during a follow-up of 679,789 person-years. Compared with no HCTZ use, the adjusted HRs for HCTZ use were 1.18 (1.00–1.40) for ≤2 years, 1.57 (1.32–1.88) for 2 to 4 years, and 2.09 (1.73–2.52) for >4 years. The HR was 0.90 (0.79–1.03) for an additional year of thiazide-like diuretic use.

**Conclusions:** In patients with diabetes, exposure to HCTZ for >2 years is associated with an increased risk of cSCC, whereas no increased risk associated with thiazide-like diuretics was observed.

**Impact:** The potential increased risk of cSCC should be a consideration when prescribing HCTZ, with thiazide-like diuretics offering a safer alternative.

## Introduction

The use of hydrochlorothiazide (HCTZ) is concerned to be at increased risk of cutaneous squamous cell carcinoma (cSCC). This is probably because of its potential to induce photosensitivity, which can lead to DNA damage and chronic inflammation (1). Despite primary cSCC having an excellent prognosis, the 10-year survival rate is only 10%–20% for those with metastatic disease (2). This is compounded by a 5-year recurrence rate of 8% for metastatic disease, doubling for large lesions (>2 cm diameter), with metastasis occurring in 25% to 45% of recurrences (2, 3). As such, cSCC not only confers high cosmetic and functional morbidity but also places considerable burden on the health care system (4, 5).

Although this concern of thiazide diuretics regarding cSCC risk has been discussed extensively in recent years (**Table 1**; refs. 6–14), this study is innovative in three aspects. Most available studies have only evaluated risk in the general population, and it remains unclear whether a diagnosis of diabetes increases the risk of skin cancer due to the resulting continuous hyperglycemia and high serum levels of insulin or insulin-like growth factor (15, 16). Over 50% of patients with type 2 diabetes (T2DM) live with hypertension (17), many of whom are prescribed the thiazide diuretic HCTZ (18). HCTZ is also frequently combined with other antihypertensive drugs, yet it is notable that the potential effect of these drugs on cSCC has not been considered. This is important when we consider that a meta-analysis has called on the need for studies to account for such antihypertensives, showing that calcium-channel blockers and β-blockers, not thiazide diuretics, are associated with 14% and 21% increased risks of skin cancer, respectively (19). Another question that remains to be answered is whether thiazide-like diuretics, a clinically alternative drug to HCTZ in the class of thiazide diuretic, would improve the cSCC risk management (20). Previous studies have mostly evaluated HCTZ and thiazide-like diuretics as a class (19, 21), resulting in limited evidence on the association of thiazide-like diuretics with the risk of cSCC.

In this study, we aimed to estimate the association of HCTZ use and the risk of cSCC among patients with T2DM, and to determine whether thiazide-like diuretics can be a safer alternative, accounting for the use of other antihypertensives.

## Materials and Methods

### Data sources

The study was conducted by data linkage from three independent databases: (i) clinical data for patients with T2DM collected annually from the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) database, (ii) cancer-related data from the Netherlands

[1]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. [2]Department of Internal Medicine, Gelre Hospital, Apeldoorn, the Netherlands. [3]Langerhans Medical Research Group, Ommen, the Netherlands. [4]Department of Research and development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands. [5]Department of Internal Medicine, Groningen, University of Groningen, University Medical Center Groningen, the Netherlands. [6]Department of Forensic Psychiatry, GGZ Drenthe Mental Health Institute, Assen, the Netherlands.

**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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**Corresponding Author:** Jing de Haan-Du, Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, Groningen 9700 RB, the Netherlands. Phone: 31-50-3610739; E-mail: j.du@umcg.nl

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**Table 1.** Overview of existing evidence on thiazide diuretics use and cutaneous squamous cell carcinoma risk.[a]

| Drug exposure | Comparator | First author | Year | Study design | Study setting | Country | Prevention of time related bias | Number of participants | Number of cSCC events | Relative risk (95% CI) | Adjusted covariates | Duration/Dosage-response relationship |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Use of HCTZ | No use of HCTZ | Jenson | 2008 | Case–control | General population | Denmark | Not reported. | Exposed: 159; Comparator: 427 | Case: 1,129; Comparator: 4,516 | Incidence rate ratios: 1.58 (1.29–1.93) | Age, sex, chronic medical conditions, use of other photosensitising diuretics and previous use of oral glucocorticoids | >1 year vs. no: 1.67 (1.36–2.07); >5 year vs. no: 1.92 (1.46–2.54) |
| | | Pedersen | 2018 | Case–control | General population | Denmark | 2 years lag time accounted. | Exposed: 1,812; Comparator: 6817 | Case: 8,629; Comparator: 172,462 | OR: 1.75 (1.66–1.85) | Age, sex, calendar time, CCI score, education, use of certain drugs, and heavy alcohol consumption, diabetes, chronic renal insufficiency, or COPD | > = 50,000 mg vs. no: 3.98 (3.68–4.31); > = 200,000 mg vs. no: 7.38 (6.32–8.60) |
| | | Han | 2020 | Cross-sectional | Patients with a history of invasive cSCC | USA | Not reported. | Exposed: 102; Comparator: 304 | Unspecified | OR: 2.21 (1.26–3.89) to have > = 20 invasive cSCC compared with <20 lifetime cSCC. | Age, sex, smoking. skin type, use of immunosuppressants, exposure to radiation, organ transplant recipients, carcinogenic exposure, PUVA or UVB treatment, outdoor exposure to sun light, use of tanning beds, and hypertension | No such analysis |
| Use of combined HCTZ[b] | No use of HCTZ | Jenson | 2008 | Case–control | General population | Denmark | Not reported. | Exposed: 154; Comparator: 372 | Case: 1,129; Comparator: 4,516 | Incidence rate ratios: 1.79 (1.45–2.21) | Same with use of HCTZ vs. no use of HCTZ by Jenson | >1 year vs. no: 1.89 (1.52–2.35); >5 year vs. no: 1.97 (1.49–2.62) |
| Use of thiazide diuretics[c] | No use of thiazide diuretics | de Vries | 2012 | Case–control | Dermatology center patients | Multiple European countries | Not reported. | Exposed: 99; Comparator: 136 | Case: 409; Comparator: 1,550 | OR: 1.66 (1.16–2.37) | Age, sex, phototype and country | No such analysis |
| Use of thiazide diuretics[d] | No use of thiazide diuretics | Robinson | 2013 | Case–control | General population | USA | Not reported. | Exposed: 239; Comparator: unknown | Case: 1,599; Comparator: 1,906 | OR: 1.30 (0.70–2.40) | Age, sex, number of painful sunburns, and study phase | Not specified for thiazide diuretics. |
| Use of thiazide diuretics[e] | No use of AD | Nardone | 2017 | Cohort | Academic center patients | USA | Not reported. | Exposed: 15,166; Comparator: 45,498 | Exposed: 130; Comparator: 132 | OR: 4.11 (2.66–6.35) | Age, sex, race and CCI score, length of follow-up, and time to event. | No such analysis |
| | | Su | 2018 | Cohort | Patients with hypertension in private health insurance | USA | Not reported. | Exposed: 10,449; Comparator: unknown | Exposed: 935; Comparator: unknown | HR: 1.09 (0.99–1.19) | Age, sex, smoking, comorbidities, history of SCC and actinic keratosis, calendar year, healthcare utilization, surveillance measure, length of health plan membership and history of photosensitizing AD use | Not specified for thiazide diuretics. |
| Use of combination thiazide diuretics[e] | No use of AD | Su | 2018 | Cohort | Patients with hypertension in private health insurance | USA | Not reported. | Exposed: 6,265; Comparator: unknown | Exposed: 579; Comparator: unknown | HR: 1.32 (1.19–1.46) | Same with Use of thiazide diuretics vs. no use of AD by Su | Not specified for thiazide diuretics. |
| >2 prescriptions of thiazide diuretics[e] | ≤2 prescriptions of any ADs | Schmidt | 2015 | Case–control | General population | Denmark | Not reported. | Exposed: 447; Comparator: 4,458 | Case: 2282; Comparator: 22,771 | OR: 1.03 (0.91–1.17) | Age, sex, county of residence, CCI score, obesity and use of systemic glucocorticoids, aspirin, non–aspirin non–steroidal anti–inflammatory drugs and statins | Not specified for thiazide diuretics. |

*(Continued on the following page)*

**Table 1.** Overview of existing evidence on thiazide diuretics use and cutaneous squamous cell carcinoma risk.[a] (Cont'd)

| Drug exposure | Comparator | First author | Year | Study design | Study setting | Country | Prevention of time related bias | Number of participants | Number of cSCC events | Relative risk (95% CI) | Adjusted covariates | Duration/Dosage-response relationship |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Use of bendroflumethiazide | No use of bendroflumethiazide | Jenson | 2008 | Case–control | General population | Denmark | Not reported. | Exposed: 241; Comparator: 913 | Case: 1129; Comparator: 4,516 | Incidence rate ratios: 1.03 (0.86–1.22) | Same with use of HCTZ vs. no use of HCTZ by Jenson | >1 year vs. no: 0.91 (0.76–1.10); >5 year vs. no: 1.03 (0.79–1.34) |
| | | Kaae | 2010 | Cohort | General population | Denmark | Not reported. | Exposed: 290,467[f]; Comparator: unknown | Exposed: 93; Comparator: unknown | Incidence rate ratios: 1.0 (0.8–1.2) | Age, sex, calendar year, education | Per 5 years of use: 1.5 (0.9–2.4) |
| Use of indapamide | No use of indapamide | Jenson | 2008 | Case–control | General population | Denmark | Not reported. | Exposed: 10; Comparator: 29 | Case: 1,129; Comparator: 4,516 | Incidence rate ratios: 1.20 (0.57–2.54) | Same with use of HCTZ vs. no use of HCTZ by Jenson | >1 year vs. no: 1.10 (0.49–2.46); >5 year vs. no: 1.02 (0.32–3.23) |

Note: Searching string: [hypertension (MeSH Terms) OR agents, antihypertensive (MeSH Terms) OR diuretics (MeSH Terms) OR thiazides (MeSH Terms)] AND [cancer, squamous cell (MeSH Terms) OR skin cancer (MeSH Terms)] and reference.

Abbreviations: AD, antihypertensive drugs; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; HCTZ, hydrochlorothiazide; SCC, squamous cell carcinoma.

[a]Because this study focused on cutaneous SCC, studies evaluated the association of HCTZ with SCC of the lip and other type of skin cancer were not included.

[b]Including HCTZ and its combination with amiloride.

[c]Not specified which thiazide diuretics, but including bendroflumethiazide.

[d]Not specified which thiazide diuretics, but including HCTZ and its combinations.

[e]Not specified which thiazide diuretics.

[f]Estimated on the basis of the total individual included in the study and the prevalence of drug usage provided in the Supplementary Materials and Methods.

Cancer Registry (NCR), and (iii) mortality data from the municipality's Personal Records Database (BRP). Data linkage was most recently performed in December 2020. According to Dutch Medical Research with Human Subjects Law (*Wet Medisch-wetenschappelijk Onderzoek met mensen*, WMO), this procedure was exempt from the need for medical ethics committee review (METC no. 13.0765).

Data in the ZODIAC database were prospectively collected from January 1998 to December 2014. At its inception, this was part of a study into the effects of structured shared care provided by specialized diabetes nurses and general practitioners (GP) for patients with T2DM (22). ZODIAC included only patients with T2DM who were exclusively treated in primary care, where more than 90% of the patients with T2DM in the Netherlands are being treated (23). After showing improved quality of care, the developed model of provision became the standard of treatment for patients with diabetes in the Zwolle region and has gradually expanded to other regions of the Netherlands, together with the accompanying data collection (22). As such, the number of GPs participating in the project increased from 53 in 1998 to 459 in 2008 and 731 in 2013 (24, 25). Specifically, the following data were collected annually in face-to-face checkups: demographic data, vital signs, medical diagnoses, medication use, lifestyle characteristics (e.g., smoking and body mass index), and laboratory results (e.g., hemoglobin A1c and serum creatinine).

The cancer and survival statuses of all patients were available by linkage with the NCR and BRP until December 31, 2019. The NCR was founded in 1989 and has since contained data for all newly diagnosed cancers in the Netherlands, except for basal cell carcinoma of the skin (26). Potential underregistration of cases has been estimated at <2% (27). The BRP contains information on all dates of death for all Dutch inhabitants (100% coverage; ref. 28). Details of the data linkage are available elsewhere (29).

## Study design and population

This prospective cohort study collected clinical data for patients with T2DM since 1998 till 2014, with follow-up data for cSCC and survival statuses ending in 2019. Cohorts with and without exposure to HCTZ and thiazide-like diuretics were compared, controlling for other antihypertensive use. To obtain a representative study population, we included all 71,648 patients from the ZODIAC database, except for those with recorded diagnosis of skin cancer in the NCR database prior to cohort entry (**Fig. 1**).

## Drug exposure

Given the complex combined therapy of hypertension treatment (Supplementary Table S1; ref. 30), and given that many of these agents are suspected of being associated with cSCC occurence (19), exposure to each antihypertensive type was accounted for in the analysis to avoid bias introduced by patient selection. To investigate potential within-class differences for thiazide diuretics, exposures to the two different drugs in this class, namely, HCTZ and thiazide-like diuretic, were defined separately. We considered the following commonly prescribed antihypertensives: HCTZ (including its combinations), thiazide-like diuretics (chlorthalidone and indapamide), angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, β-blockers, and other diuretics (loop diuretics and potassium-sparing diuretics).

Drug-induced photosensitivity is a duration- or dose-sensitive reaction (**Table 1**), so we defined drug exposure by time-dependent cumulative exposure. This was the sum of all known years of usage for a given antihypertensive, and as such, the cumulative exposure was zero for patients who did not use that drug. If there was a missing year

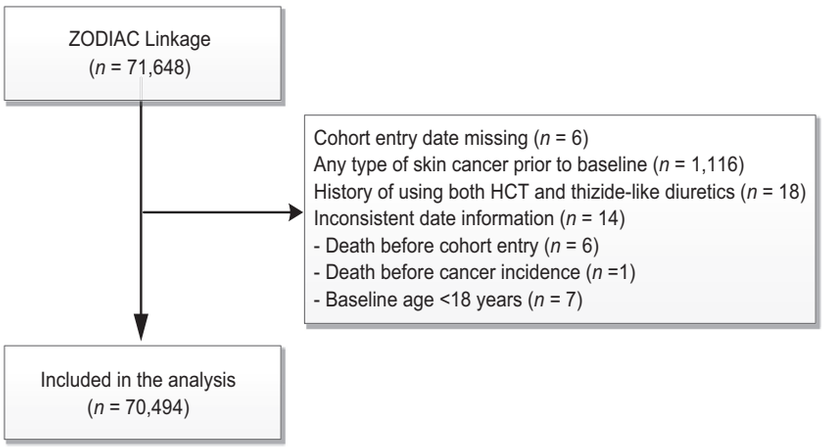


**Figure 1.**
Study flow chart for data linkage and inclusion for analysis. ZODIAC was linked with the Dutch National Cancer Registration for cancer cases and the municipality's Personal Records Database for death information. The ZODIAC cohort contains clinical data from January 1998 to December 2014. The linkage procedure of these three databases was last performed in December 2020, at which time cancer events and death events were observable up to December 31, 2019. HCT, hydrochlorothiazide; ZODIAC, the Zwolle Outpatient Diabetes project Integrating Available Care.

between 2 years of known usage, the previous cumulative duration was carried forward to the missing year. Drug exposure was only collected to the end of 2014, so we carried forward cumulative drug exposure from 2014 to subsequent years.

### Definitions

The baseline date was that of cohort entry for each patient. Follow-up ended for each patient on the first skin cancer incident, the date of death, or December 31, 2019, whichever occurred first.

### Baseline covariates

The predefined confounders were age, sex, diabetes duration, smoking, systolic blood pressure, body mass index (31), serum creatinine (32), baseline year, and use of sulphonylureas (1), metformin (33), aspirin or other nonsteroidal anti-inflammatory drugs (34), and statins (35). Smoking was categorized into ever smokers, never smokers, and unknown. We set diabetes duration, body mass index, systolic blood pressure, and serum creatinine as continuous variables.

### Study outcome measure

The primary outcome measure was the relative risk of cSCC for exposure to HCTZ compared with no expose to HCTZ. The secondary outcome was the relative risk of cSCC for exposure to thiazide-like diuretics compared with no expose to thiazide-like diuretics.

### Statistical analysis

Descriptive analyses are reported by baseline exposure to HCTZ as proportions, medians with interquartile ranges (IQR), or as means and SDs, as appropriate. All statistical tests were two sided and conducted at the 5% significance level. STATA software (version 15.0, StataCorp) was used for all statistical analyses.

A time-dependent Cox proportional hazards model was constructed to estimate the study outcomes. The cumulative duration of HCTZ usage was categorized as ≤2 years, 2 to 4 years, and >4 years based on its distribution and was entered into the model in a time-dependent way. For example, if a patient had used HCTZ for >4 years in total and was diagnosed with cSCC in the third year, this cSCC event was attributed to the exposure category of 2 to 4 years. The same categorization was planned for cumulative exposure to thiazide-like diuretics to evaluate whether thiazide-like diuretics were a safer alternative. However, this was not possible due to the limited number of thiazide-like diuretic users, so it was included in the analysis as a continuous variable. The model was further adjusted by time-updated cumulative exposure to each antihypertensive drug (continuous variables) and all baseline covariates. Age was used as a timescale for all models to account for its effect on risk (36). Stratification by baseline year was used to account for the effect of different cohort entry years. The proportional hazards assumptions were checked by plotting and testing Schoenfeld residuals. A 1-year lag period was applied (37), thereby discounting cases of skin cancer within half a year after baseline. Missing values were deemed to be missing completely at random, as the cause of missing values (e.g., a patient moved or emigrated) seemed unlikely to be dependent on either the exposure or the outcome and the missing could not be explained by observed data. To make full use of the available data, a total of 16% missing values for body mass index, systolic blood pressure, and serum creatinine at baseline were imputed by multiple imputation (20 times; ref. 38).

### Sensitivity analyses

First, to gain as representative a population as possible, both prevalent and incident antihypertensive drug users were included in the primary analysis. This was because the date of first antihypertensive use was not available and only including patients who started drugs after cohort entry could have led to a highly selected population of newly antihypertensive drug users who were diagnosed with hypertension after their diabetes diagnosis. To account for patients using an antihypertensive at cohort entry, who may already have had several years of drug use that could impact our results, we conducted a sensitivity analysis for known new users. We defined these known new users as those who first used antihypertensives after cohort entry. Second, we reconstructed the model using a lag time of 2 years for cSCC occurrence. Third, to account for unknown drug exposure between 2014 and 2019, analysis was repeated with the end of follow-up censored on December 31, 2014. Finally, we performed an analysis that included only complete cases with no missing baseline covariates.

### *Post hoc* analysis

As time-dependent drug exposure might be influenced by other factors associated with the outcome, to avoid this potential uncontrolled confounding (39), we repeated all the analysis by categorizing each antihypertensive drug use into "Ever" and "Never" use.

## Results

We included 70,494 patients with a median follow-up of 10 (IQR: 8–13) years, providing follow-up data for 679,789 person-years. Among these, 1,409 cSCC events occurred, giving an incidence of 207.3 (95%

**Table 2.** Baseline patient characteristics of patients with type 2 diabetes.

| Characteristics | Baseline HCTZ | | P |
|---|---|---|---|
| | Yes ($n$ = 11,165) | No ($n$ = 59,329) | |
| Age (years) | 67.6 ± 11.0 | 65.4 ± 12.3 | <**0.001** |
| Male, *n* (%) | 4,618 (41.4) | 30,927 (52.1) | <**0.001** |
| Duration of diabetes (years) | 2.4 (0.3–5.9) | 2.6 (0.2–6.2) | **0.008** |
| Serum creatinine (μmol/L) | 76 (65–90)[a] | 76 (65–89)[b] | **0.017** |
| BMI (kg/cm$^2$) | 30.5 ± 5.4[c] | 29.7 ± 5.3[d] | <**0.001** |
| Smoking, *n* (%) | | | |
| No | 8,118 (72.7) | 39,379 (66.4) | <**0.001** |
| Ever | 2,199 (19.7) | 12,614 (21.3) | |
| Unknown | 848 (7.6) | 7,336 (12.4) | |
| Systolic blood pressure (mmHg) | 143.8 ± 17.6[e] | 139.0 ± 18.1[f] | <**0.001** |
| Use of metformin, *n* (%) | 6,410 (57.4) | 33,287 (56.1) | **0.011** |
| Use of sulphonylureas, *n* (%) | 3,036 (27.2) | 17,833 (30.1) | <**0.001** |
| Use of Lipid-lowering drugs, *n* (%) | 7,085 (63.5) | 32,573 (54.9) | <**0.001** |
| Use of NSAIDs, *n* (%) | 730 (6.5) | 3,247 (5.5) | <**0.001** |
| Use of other ADs, *n* (%) | | | |
| ACEi | 4,517 (40.5) | 12,718 (21.4) | <**0.001** |
| ARB | 2,243 (20.1) | 5,860 (9.9) | <**0.001** |
| Beta blockers | 4,945 (44.3) | 14,602 (24.6) | <**0.001** |
| CCB | 2,486 (22.3) | 7,821(13.2) | <**0.001** |
| Thiazide-like-diuretics | 0 (0) | 930 (1.6) | <**0.001** |
| Other diuretics | 317 (2.8) | 5,429 (9.2) | <**0.001** |

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitors; AD, antihypertensive drugs; ARB, angiotensin-receptor blockers; BMI, body mass index; CCB, calcium-channel blockers; HCTZ, hydrochlorothiazide; NSAID, nonsteroidal anti-inflammatory drugs. Normally distributed variables presented as mean ± SD. Non-normally distributed data presented as median (interquartile range).
[a]746 missing.
[b]5,856 missing.
[c]759 missing.
[d]6,243 missing.
[e]255 missing.
[f]2,495 missing.

confidence interval: 196.7–218.4) per $10^5$ person-years. **Table 2** presents the characteristics of the study population by HCTZ use at baseline. Patients using HCTZ tended to be older, have higher systolic blood pressure, and to be more likely to use other antihypertensives, but were less often male and smokers.

**Table 3** presents the relative risk of cSCC in the primary and the sensitivity analyses. HCTZ use for >2 years was consistently associated with an increased risk of cSCC compared with no HCTZ use. Longer exposure tended to increase the risk, except when HCTZ use >4 years was compared with no HCTZ use among known new antihypertensive users. No increased risk of cSCC was observed after an additional year of thiazide-like diuretic use, another type of thiazide diuretics, in the primary or sensitivity analyses.

Supplementary Table S2 shows the estimated HRs for the covariates. An additional year of β-blocker use was associated with a 6%–7% increased risk of cSCC in all analyses, except for the sensitivity analysis that only included known new antihypertensive users. One-unit increases in the body mass index and being female were associated with a 2% and a 20%–32% lower risk of cSCC, respectively. Given that women showed a lower risk of cSCC incidence compared with men, the possible interactions of sex and HCTZ exposure, sex and thiazide-like diuretics exposure were tested in the full model, respectively. No significant interaction effect was observed. Supplementary Table S3 presents the results for the *post hoc* analyses of defining drug exposure by "Ever" and "Never" use, showing consistent results with defining cumulative drug exposure in a time-dependent manner.

# Discussion

This study firstly assessed the association of HCTZ use with cSCC risk among patients with T2DM, accounting for the use of other antihypertensives. We observed an exposure time–response relationship for HCTZ use, with the risk of cSCC increasing by half at 2 to 4 years and doubling at >4 years compared with no HCTZ use. Notably, no increased risk of cSCC after an additional year of using thiazide-like diuretics, a clinically viable alternative to HCTZ, although limited to small number of cSCC events, was observed. Sensitivity analyses and *post hoc* analyses confirmed the results of the primary analyses.

### Comparison with literature

To date, nine studies have investigated the association of thiazide diuretic use and cSCC risk (**Table 1**; refs. 6–14). Only two case–control studies specifically evaluated the effect of HCTZ (alone or in combination), showing a consistent and significant increased risk of 58% to 79% compared with not using HCTZ (6, 7). In one, a duration-response relationship was even evident after a year of use (7). A recent cross-sectional study showed that HCTZ use was associated with a 121% increased risk of being high SCC burden (≥20 invasive history of cSCC) compared with non-high SCC burden (<20 history of cSCC; ref. 14). Most studies evaluated thiazide diuretics as a class without specifying the individual drugs (8, 10–13). Two showed a nonsignificantly increased risk of 3% to 30% (10, 11), while the other three

**Table 3.** Relative risk of squamous cell skin cancer among patients with T2DM using HCTZ.

| Drug use | Patients (*n*) | SCC (*n*)[b] | PYS | Incidence rate per $10^5$ PYS | Adjusted by sex and baseline year HR (95%CI) | Full model[c] HR (95%CI) |
|---|---|---|---|---|---|---|
| Primary analysis | | | | | | |
| No HCTZ[a] | 51,965 | 896 | 509,729 | 175.8 (164.7–187.7) | 1.00 | 1.00 |
| ≤2 years | 7,279 | 165 | 77,724 | 212.3 (182.3–247.2) | 1.10 (0.93–1.29) | 1.18 (1.00–1.40) |
| 2–4 years | 5,778 | 163 | 51,859 | 314.3 (269.7–366.4) | **1.52 (1.28–1.80)** | **1.57 (1.32–1.88)** |
| >4 years | 5,472 | 185 | 40,477 | 457.1 (395.8–527.7) | **2.04 (1.71–2.44)** | **2.09 (1.73–2.52)** |
| Thiazide-like diuretics use per year | 1,648 | 23 | 16,927 | 135.9 (90.3–204.4) | 0.89 (0.78–1.02) | 0.90 (0.79–1.03) |
| Known new users | | | | | | |
| No HCTZ[a] | 26,327 | 390 | 265,914 | 146.7 (132.8–162.0) | 1.00 | 1.00 |
| ≤2 years | 1,804 | 37 | 17,817 | 207.7(150.5–286.5) | 1.24 (0.88–1.74) | 1.37 (0.97–1.93) |
| 2–4 years | 1,106 | 29 | 9,688 | 299.3 (208.1–430.5) | **1.54 (1.04–2.28)** | **1.62 (1.08–2.45)** |
| >4 years | 995 | 22 | 7,276 | 302.4 (199.2–458.9) | 1.42 (0.89–2.26) | 1.43 (0.86–2.36) |
| Thiazide-like diuretics use per year | 450 | 3 | 4,750 | 63.2 (20.4–195.8) | 0.78 (0.54–1.12) | 0.82 (0.57–1.17) |
| 2 year lag period | | | | | | |
| No HCTZ[a] | 51,965 | 813 | 509,729 | 159.5 (148.9–170.8) | 1.00 | 1.00 |
| ≤2 years | 7,279 | 142 | 77,724 | 182.7 (155.0–215.3) | 1.03 (0.86–1.24) | 1.11 (0.92–1.33) |
| 2–4 years | 5,778 | 155 | 51,859 | 298.9 (255.4–349.8) | **1.57 (1.31–1.87)** | **1.61 (1.34–1.94)** |
| >4 years | 5,472 | 185 | 40,477 | 457.1 (395.8–527.7) | **2.12 (1.76–2.54)** | **2.14 (1.77–2.60)** |
| Thiazide-like diuretics use per year | 1,648 | 21 | 16,927 | 124.1 (80.9–190.2) | 0.89 (0.78–1.02) | 0.90 (0.78–1.03) |
| Data till 2014 | | | | | | |
| No HCTZ[a] | 51,965 | 410 | 300,682 | 136.4 (123.8–150.2) | 1.00 | 1.00 |
| ≤2 years | 7,279 | 71 | 49,340 | 143.9 (114.1–181.6) | 0.98 (0.76–1.26) | 1.06 (0.82–1.38) |
| 2–4 years | 5,778 | 71 | 28,091 | 252.8 (200.4–318.9) | **1.59 (1.23–2.06)** | **1.73 (1.32–2.27)** |
| >4 years | 5,472 | 68 | 18,216 | 373.3 (294.5–473.3) | **2.12 (1.58–2.85)** | **2.31 (1.69–3.14)** |
| Thiazide-like diuretics use per year | 1,648 | 8 | 10,224 | 78.3 (39.1–156.4) | 0.86 (0.68–1.08) | 0.87 (0.69–1.10) |
| Complete cases | | | | | | |
| No HCTZ[a] | 42,458 | 750 | 410,318 | 182.8 (170.2–196.3) | 1.00 | 1.00 |
| ≤2 years | 6,033 | 144 | 63,747 | 225.9 (191.9–265.9) | 1.13 (0.95–1.35) | 1.15 (0.96–1.38) |
| 2–4 years | 5,074 | 142 | 44,730 | 317.5(269.4–374.1) | **1.51 (1.26–1.82)** | **1.55 (1.29–1.87)** |
| >4 years | 4,568 | 149 | 33,632 | 443.0 (377.5–520.0) | **1.95 (1.60–2.38)** | **1.99 (1.63–2.43)** |
| Thiazide-like diuretics use per year | 1,414 | 21 | 14,103 | 148.9 (97.1–228.4) | 0.92 (0.80–1.05) | 0.93 (0.81–1.06) |

Abbreviations: CI, confidence interval; HCTZ, hydrochlorothiazide; HR, hazard ratio; PYS, person–years; SCC, squamous cell carcinoma; T2DM, type 2 diabetes.
[a]No use of HCTZ throughout the follow-up.
[b]Numbers were presented in a dynamic manner, for example, cases for "No HCTZ" included all the cSCC developed when a patient were not using HCTZ.
[c]Adjusted for baseline covariates: sex, smoking (yes/no, not known), body mass index, systolic blood pressure, serum creatinine, use of sulphonylureas, use of metformin, use of lipid lowering drugs, and use of non–steroidal anti–inflammatory drugs. Number in bold means a significant difference at $P < 0.05$ level. For all the models, age was used as the timescale and baseline year was used as a stratification variable. For all the models the cumulative use of other antihypertensive drugs including angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, β blockers, and other diuretics except for HCTZ were adjusted as a time-updated continuous variable.

showed a significantly increased risk of 32% to 311% (8, 12, 13); however, no duration-response relationship was specified for the thiazide diuretic class. In two studies that evaluated bendroflumethiazide and indapamide separately (7, 9), neither of the thiazide diuretics was associated with a significantly increased risk of cSCC or a significant duration-response relationship.

Our result on the association of HCTZ and cSCC risk was consistent with previously reported data. That said, we observed the association after 2 years of known HCTZ exposure, while the previous data only reported this association from 1 year of exposure. This might because existing reports did not account for time-related bias. Of note, our study population also included patients with diabetes in whom the risk of skin cancer might be increased (15) and treatment with metformin may be protective (35). Concerning the association of thiazide-like diuretics with cSCC risk, bendroflumethiazide was not used in our cohort, so we could not compare with this dominantly reported thiazide diuretic. In our analyses, thiazide-like diuretic use (indapamide and chlorthalidone) was not associated with an increased risk of cSCC, but data from the literature indicate that there is a nonsignificant 20% increased risk among indapamide users (7). This 20% increased risk arose in 39 patients (0.7%) from a case–control design that failed to account for time-related bias, potentially causing the difference.

### Photosensitizing mechanism

The association between HCTZ and cSCC can be explained by drug-induced photosensitivity permitting the absorption of ultraviolet radiation. This could promote sunburn, may be carcinogenic, may trigger phototoxic or photoallergic reactions, and may induce DNA damage and chronic inflammation (40). A sulfonamide moiety, the shared chemical structure of all diuretics, was suspected to explain the photosensitizing characteristic of these drugs (1). If this mechanism held true, an increased risk of cSCC would be expected among thiazide-like diuretics users. However, we found that thiazide-like diuretics were not, whereas β-blockers were, associated with an increased risk of cSCC. This warrants future investigation to assess the potential risk of β-blockers use and implies that the sulfonamide

moiety does not fully explain the increased risk of cSCC with HCTZ use, requiring further studies to determine the underlying mechanism. Furthermore, future studies on related outcomes, such as the stage of SCC and SCC origins from other parts of the body, are of important value to better understand the mechanism.

### Strengths and limitations

This study has several strengths. More than 90% of patients with T2DM in the Netherlands are treated in primary care, meaning that the results for this cohort can be generalized to most patients with T2DM in the Netherlands. The use of other antihypertensives was also accounted for separately in the analysis of patients with diabetes, as were other relevant covariates (e.g., systolic blood pressure, serum creatinine, and the use of drugs that may affect skin cancer risk). Thiazide-like diuretic use was also evaluated separately from HCTZ as a potential alternative, providing important knowledge that can guide practice and further study. Unlike currently available data, we also attempted to prevent time-related bias by allowing a lag time of 1–2 years and by defining drug exposure time dependently.

Several limitations should be considered when interpreting our results. First, the date of first antihypertensive use was unavailable, which precluded analysis by time since first use. The hazard ratios generated for known new users tended to be higher than those in the primary analysis when there were enough events, consistent with our expectation that we could underestimate the HRs because of uncounted drug exposure before cohort entry. Second, sun exposure and skin phenotype (i.e., skin sensitivity to sunlight), key triggering factors, were not accounted for because this information was not available. Nevertheless, the use of HCTZ or another type of antihypertensive was likely to be independent of these factors. Third, we identified only a small number of thiazide-like diuretic users in the cohort, which limited our evaluation to their duration-exposure relationship. This might result from the fact that many patients had started HCTZ when a thiazide diuretic was first indicated or that thiazide-like diuretics were in limited supply (41). Fourth, accurate dosage information was unavailable, precluding analysis of the dose–response relationship. Fifth, annual data collection meant that drug exposure could only be evaluated at the year level, whereas a more accurate estimate could be generated with monthly or daily collection. Finally, the observational study design means that some confounders may not have been measured, such as HIV and alcohol consumption, but we do not expect a relevant difference among the antihypertensives used.

### Conclusions

In this Dutch cohort of patients with T2DM, an exposure time–response relationship was observed between HCTZ exposure and the risk of cSCC, while thiazide-like diuretic use did not appear to be associated with an increased risk. These results suggesting that thiazide-like diuretics may offer a safer alternative to HCTZ. Future studies are needed to confirm the observed association.

## Authors' Disclosures

No disclosures were reported.

## Authors' Contributions

**J. de Haan-Du:** Conceptualization, formal analysis, funding acquisition, investigation, methodology, writing–original draft, project administration. **G.W.D. Landman:** Conceptualization, resources, supervision, funding acquisition, investigation, methodology, writing–review and editing. **K.H. Groenier:** Formal analysis, supervision, investigation, methodology, writing–review and editing. **P.A.J. Vissers:** Writing–review and editing. **M.W.J. Louwman:** Writing–review and editing. **N. Kleefstra:** Resources, supervision, investigation, writing–review and editing. **G.H. de Bock:** Conceptualization, resources, supervision, funding acquisition, methodology, writing–review and editing.

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