Association between hydrochlorothiazide and the risk of in situ and invasive squamous cell skin carcinoma and basal cell carcinoma: A population-based case-control study

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Background: Population-based studies analyzing hydrochlorothiazide's (HCTZ's) effect on keratinocyte carcinoma, and particularly invasive squamous cell carcinoma (SCC), are lacking.

Objectives: To characterize the association between HCTZ use and invasive SCC, SCC in situ (SCCis), and basal cell carcinoma (BCC).

Methods: This population-based case-control study included all 6880 patients diagnosed with first-time BCC, SCCis, and invasive SCC between 2003 and 2017 in Iceland and 69,620 population controls. Conditional logistic regression analyses were used to calculate multivariate odds ratios (ORs) for keratinocyte carcinoma associated with HCTZ use.

Results: A cumulative HCTZ dose above 37,500 mg was associated with increased risk of invasive SCC (OR, 1.69; 95% confidence interval [CI], 1.04-2.74). Users of HCTZ also had an increased risk of SCCis (OR, 1.24; 95% CI, 1.01-1.52) and BCC (OR, 1.14; 95% CI, 1.02-1.29).

Limitations: Limitations include this study's retrospective nature with the resulting inability to adjust for ultraviolet exposure, Fitzpatrick skin type, and comorbidities.

Conclusions: High cumulative exposure to HCTZ is associated with the development of keratinocyte carcinoma and, most importantly, invasive SCC. Sun protective behaviors alone may not eliminate the carcinogenic potential of HCTZ. (J Am Acad Dermatol 2021;84:669-75.)

Key words: basal cell carcinoma; epidemiology; hydrochlorothiazide; keratinocyte carcinoma; squamous cell carcinoma.

There is increasing evidence suggesting an association between hydrochlorothiazide (HCTZ) exposure and the development of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[1,2] Whether HCTZ has a causal effect on the development of keratinocyte carcinoma

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is of great interest because HCTZ is one of the most commonly prescribed antihypertensives in Europe and North America.[2,3] HCTZ is a known photosensitizer and is thought to contribute to the development of keratinocyte carcinoma by causing the production of free radicals and reactive oxygen species upon exposure to ultraviolet (UV) radiation.[2] The effect of HCTZ in low-UV environments is unknown, and the identification of strong epidemiologic data supporting a causal association between HCTZ use and keratinocyte carcinoma development would help guide initial antihypertensive management in patients at high risk of developing keratinocyte carcinoma.

To date, 3 population-based case-control studies and several smaller case-control and cohort studies have evaluated the association between HCTZ and keratinocyte carcinoma.[1,4-12] However, the results from these studies were conflicting. As a result, no clear clinical recommendations have been developed based on their findings.[13] Previous studies were limited by small sample size, inconsistent definitions of exposure (HCTZ alone, HCTZ in combination with other medications, or all thiazide diuretics), and different outcome measures (SCC, BCC, or keratinocyte carcinoma).

We present a population-based study analyzing the association between keratinocyte carcinoma and HCTZ in Iceland. This study covering the entire Icelandic population is a unique addition to previous studies because (1) Iceland's population is homogenous[14,15]; (2) Reykjavik, Iceland's capital, is the northernmost capital in the world, with very low levels of daily ambient UV radiation[16]; (3) Iceland is a small country with minimal variation in daily ambient UV exposure[17]; and (4) the Icelandic Cancer Registry (ICR) separately classifies squamous cell carcinoma in situ (SCCis) from invasive SCC, allowing this study to be the first to assess HCTZ's relationship with each of these prognostically distinct entities[18]; (5) The Icelandic Prescription Medicine Register is a population-based registry that records all outpatient prescriptions and can be directly linked to the ICR.[19]

CAPSULE SUMMARY

- High cumulative hydrochlorothiazide (HCTZ) exposure is associated with an increased risk of keratinocyte carcinoma and, particularly, invasive squamous cell carcinoma.
- Patients on long-term HCTZ treatment should be counseled about the risk of developing keratinocyte carcinoma. Because average sun protection alone may not eliminate HCTZ's carcinogenic potential, practitioners may consider switching patients to other first-line antihypertensives.

METHODS

This is a population-based case-control study. The group of cases consisted of all individuals diagnosed for the first time with SCCis, invasive SCC, and BCC of the skin with histologic confirmation in Iceland between 2003 and 2017. For each case, 10 unaffected population control individuals, matched by year of birth and sex, were randomly selected from the National Register of Iceland.

Two nationwide databases were used to extract data about keratinocyte carcinoma diagnosis and prescription drug use in Iceland. The ICR records all cases of skin cancer diagnosed with histologic verification.[18] The Icelandic Prescription Medicine Register is run by the Directorate of Health and records all electronic outpatient prescriptions since 2002.[19] Demographic data, including Charleston Comorbidity Index, ethnicity, smoking status, and socioeconomic status, were not available for analysis. By record linkage using the unique personal identification number, all HCTZ prescriptions for case patients and control individuals were identified from the Icelandic Prescription Medicine Register.

The index date was defined as the date of keratinocyte carcinoma diagnosis. Patients were considered exposed to HCTZ if they had filled 1 or more HCTZ prescriptions at least 2 years before the index date. Prescriptions of HCTZ filled less than 2 years before the index date were disregarded to account for possible lag time of HCTZ affecting the risk of developing keratinocyte carcinoma. We chose to implement a 2-year lag time because it has been shown in other similar studies that increased lag time is associated with increasing SCC risk.[4] Prescriptions filled less than 2 years before diagnosis were unlikely to have affected the risk of keratinocyte carcinoma because photosensitization is a chronic process that takes multiple years.[20] For all patients, cumulative exposure to HCTZ was recorded in daily dose units (DDU) and milligrams. A DDU is the average daily maintenance dose of a drug when used for its primary indication.[21] Patients taking azathioprine, mycophenolate mofetil, and cyclosporine were subsequently excluded as these immunosuppressive medications dramatically increase the risk of keratinocyte carcinoma.[20]

Conditional logistic regression analyses were performed to determine multivariate odds ratios (ORs) with 95% confidence intervals (CI) for the

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
DDU:	daily dose unit
HCTZ:	hydrochlorothiazide
ICR:	Icelandic Cancer Registry
OR:	odds ratio
SCC:	squamous cell carcinoma
SCCis:	squamous cell carcinoma in-situ
UV:	ultraviolet

association between HCTZ use and the likelihood of BCC, invasive SCC, and SCCis. ORs were adjusted for the use of tetracyclines and topical and oral retinoids because these are photosensitizing medications that independently increase the risk of keratinocyte carcinoma.[20] Invasive SCC, SCCis, and BCC were evaluated separately in all analyses, with never users of HCTZ serving as the control for all cases. Trend analysis was used to assess for a dose-response relationship for each tumor subtype. *P* values of the tests were calculated by using weighted linear regression, which regressed ORs based on the median dosage for each HCTZ dose category (1-500, 501-1500, and >1500 DDU). The inverse variance of the log-effect size was used as weight.[22] A *P* value of less than .05 was considered statistically significant. The study protocol was approved by the Icelandic National Bioethics Committee (VSNb2018030013).

RESULTS

Altogether, 1013 patients with invasive SCC, 1167 with SCCis, and 4700 with BCC were identified and were age- and sex-matched with 10,367; 11,961; and 47,292 control individuals, respectively. Patient characteristics are described in Table I. Male patients constituted 42%, 36%, and 51% of patients with BCC, SCCis, and invasive SCC, respectively.

The relationship between HCTZ exposure and keratinocyte carcinoma risk is reported in Table II and Fig 1. Of individuals with invasive SCC, 8.9% were users of HCTZ as compared to 8.6% of control individuals. At low and moderate doses of HCTZ, there was no difference in invasive SCC risk between HCTZ users and control individuals. Cumulative HCTZ doses greater than 1500 DDU (37,500 mg) were associated with an increased risk of invasive SCC (OR, 1.69; 95% CI, 1.04-2.74).

Similarly, 10.0% of individuals diagnosed with SCCis were users of HCTZ as compared to 8.2% of control individuals. Users of HCTZ showed a significant increase in SCCis risk as compared to control individuals (OR, 1.24; 95% CI, 1.01-1.52).

Additionally, 7.4% of individuals diagnosed with BCC were users of HCTZ compared to 6.5% of control individuals. HCTZ use was associated with an increased risk of developing BCC (OR, 1.14; 95% CI, 1.02-1.29). The dose-response relationship was statistically significant for BCC ($P = .02$) but not for SCCis ($P = .64$) or for invasive SCC ($P = .1$) (Fig 1).

Subgroup analysis was performed (Table III). HCTZ use was associated with a significant increase in risk of SCCis in male patients and people aged 50 years and older (OR, 1.45; 95% CI, 1.03-2.04 and OR, 1.23; 95% CI, 1.00-1.52, respectively). Similarly, HCTZ use was associated with a significant increase in BCC risk in people aged 50 years and older (OR, 1.15; 95% CI, 1.02-1.30).

DISCUSSION

This population-based Icelandic study, which includes more than 1000 patients with invasive SCC, 1100 patients with SCCis, and 4700 patients with BCC, supports an association between HCTZ use and all 3 types of keratinocyte carcinoma studied herein. This study is well suited to show an association between HCTZ use and keratinocyte carcinoma because of Iceland's unique demographics, low average daily ambient UV exposure, and stringent recording of keratinocyte carcinoma cases.

The Icelandic population is exceptionally homogenous with minimal variance in Fitzpatrick skin type among Icelanders.[15] Close to 100% of Icelanders are white.[14] In contrast, Denmark, where a similar population-based cohort study was performed, is more genetically heterogeneous.[15] Because Fitzpatrick skin type is a major determinant of skin cancer risk at the population level, Iceland's homogeneity strongly contributes to the study's internal validity. Although South Korea, where a population-based cohort study was also performed, is also ethnically homogenous, the incidence of keratinocyte carcinoma in South Koreans is approximately 24 to 40 times lower than the incidence of keratinocyte carcinoma in Iceland, due in large part to ethnic differences between the populations.[12]

Additionally, our data suggest that relatively low levels of average daily UV exposure are sufficient to observe an association between HCTZ exposure and keratinocyte carcinoma development. As mentioned previously, Reykjavik, Iceland's capital, is the northernmost capital in the world.[16] The average daily UV exposure in Iceland is 957 J/m^2, which is roughly half of Denmark's exposure (1691 J/m^2), and one third that of South Korea and the United States (2535 J/m^2

Table I. Characteristics of patients with BCC, SCCis, and invasive SCC and age- and sex-matched control individuals

	BCC		SCCis		Invasive SCC	
Characteristics	Case patients (n = 4700)	Control individuals (n = 47,292)	Case patients (n = 1167)	Control individuals (n = 11,961)	Case patients (n = 1013)	Control individuals (n = 10,376)
Age, y, median (IQR)	69 (56-79)	69 (56-79)	77 (67-84)	77 (67-84)	79 (71-85)	79 (70-85)
Male sex, n (%)	1988 (42.3)	20,022 (42.3)	425 (36.4)	4368 (36.5)	521 (51.4)	5309 (51.2)
Use of HCTZ, n (%)						
Never use	4354 (92.6)	44,226 (93.5)	1051 (90.1)	10982 (91.8)	923 (91.1)	9473 (91.4)
Ever use	346 (7.4)	3066 (6.5)	116 (10.0)	979 (8.2)	90 (8.9)	894 (8.6)

BCC, Basal cell carcinoma; *HCTZ*, hydrochlorothiazide; *IQR*, interquartile range; *SCC*, squamous cell carcinoma; *SCCis*, in situ squamous cell carcinoma.

Table II. Association between HCTZ use and risk of BCC, SCCis, and invasive SCC

Subgroup	Case patients	Control individuals	OR (95% CI)	Adjusted OR (95% CI)*
BCC				
Never use, n	4354	44,226	1.00	1.00
Ever use	346	3066	1.15 (1.02-1.30)	1.14 (1.02-1.29)
Cumulative dosage, n				
1-500 DDU (25-12,500 mg)	210	1981	1.08 (0.93-1.25)	1.07 (0.93-1.24)
501-1500 DDU (12,525-37,500 mg)	87	734	1.22 (0.97-1.53)	1.21 (0.97-1.52)
>1500 DDU (>37,500 mg)	49	351	1.43 (1.06-1.94)	1.42 (1.05-1.92)
BCC continuous trend test	*P* = .02			
SCCis				
Never use, n	1051	10,982	1.00	1.00
Ever use, n	116	979	1.24 (1.01-1.53)	1.24 (1.01-1.52)
Cumulative dosage, n				
1-500 DDU (25-12,500 mg)	68	639	1.12 (0.86-1.45)	1.11 (0.86-1.45)
501-1500 DDU (12,525-37,500 mg)	32	215	1.55 (1.06-2.26)	1.55 (1.06-2.26)
>1500 DDU (>37,500 mg)	16	125	1.34 (0.79-2.28)	1.35 (0.79-2.29)
SCCis continuous trend test	*P* = .64			
Invasive SCC				
Never use, n	923	9473	1.00	1.00
Ever use, n	90	894	1.03 (0.82-1.30)	1.02 (0.81-1.29)
Cumulative dosage, n				
1-500 DDU (25-12,500 mg)	49	568	0.88 (0.65-1.20)	0.87 (0.64-1.18)
501-1500 DDU (12,525-37,500 mg)	21	205	1.05 (0.67-1.66)	1.05 (0.66-1.66)
>1500 DDU (>37,500 mg)	20	121	1.67 (1.03-2.71)	1.69 (1.04-2.74)
Invasive SCC continuous trend test	*P* = .1			

BCC, Basal cell carcinoma; *CI*, confidence interval; *DDU*, daily dose unit; *HCTZ*, hydrochlorothiazide; *OR*, odds ratio; *SCC*, squamous cell carcinoma; *SCCis*, in situ squamous cell carcinoma.
*Model adjusted for the use of the following photosensitizing medications: tetracyclines, oral retinoids, and topical retinoids.

and 2736 J/m^2).[23] Furthermore, because of Iceland's small size of 39,769 square miles and approximately 3° range of latitude from its northernmost to southernmost tips, average daily ambient UV exposure is relatively consistent throughout the country.[24] Tanning bed use is commonplace in Iceland, with 70% of women and 35% of men having used a tanning bed.[16] Foreign travel is also common and has been increasing in recent years.[16] It is likely that these 2 factors play an important part in the UV exposure of this population.

SCCis and invasive SCC

To our knowledge, this study is the first to analyze the association between HCTZ and the risk of invasive SCC and SCCis separately. This is important because invasive SCC has a more aggressive disease course compared to SCCis. Our study was able to distinguish between these entities because the ICR records these histopathologic diagnoses separately.[18] We identified independent associations between invasive SCC and SCCis with HCTZ use. Only patients with the highest exposures

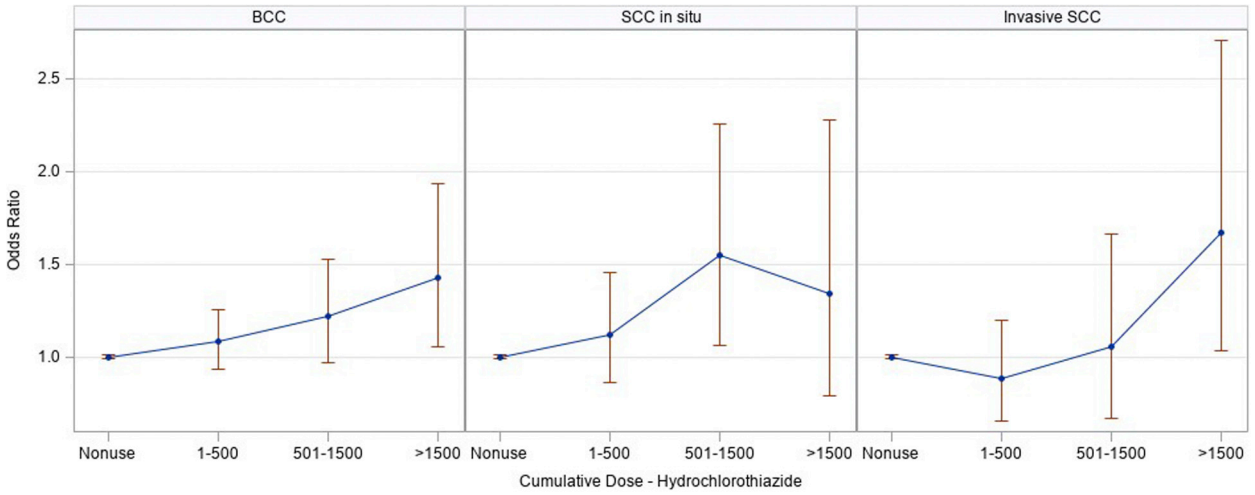

Fig 1. Dose-response relationships between cumulative HCTZ dosage and risk of BCC, SCCis, and invasive SCC. A continuous trend test resulted in *P* values of .02, .64, and .1, respectively.

Table III. Associations of HCTZ use and keratinocyte carcinoma by subgroup

Subgroup	Case patients, n (exposed/unexposed)	Control individuals, n (exposed/unexposed)	OR (95% CI)	Adjusted OR (95% CI)
BCC				
Male	136/1852	1226/18,796	1.13 (0.94-1.37)	1.12 (0.93-1.36)
Female	210/2502	1840/25,430	1.16 (1.00-1.36)	1.16 (0.99-1.35)
<50 y	7/740	73/7445	0.97 (0.44-2.12)	0.72 (0.61-0.86)
≥50 y	339/3614	2993/36,781	1.16 (1.03-1.30)	1.15 (1.02-1.30)
SCCis				
Male	44/381	328/4040	1.45 (1.04-2.04)	1.45 (1.03-2.04)
Female	72/670	651/6942	1.14 (0.88-1.48)	1.13 (0.87-1.47)
<50 y	1/63	4/671	2.65 (0.27-26.29)	2.21 (0.21-22.94)
≥50 y	115/988	975/10,311	1.24 (1.00-1.52)	1.23 (1.00-1.52)
Invasive SCC				
Male	39/482	389/4920	1.01 (0.71-1.43)	1.01 (0.71-1.43)
Female	51/441	505/4553	1.05 (0.77-1.43)	1.03 (0.75-1.41)
<50 y	0/35	0/380	—	—
≥50 y	90/888	894/9093	1.03 (0.82-1.30)	1.021 (0.810-1.29)

BCC, Basal cell carcinoma; *CI*, confidence interval; *HCTZ*, hydrochlorothiazide; *OR*, odds ratio; *SCC*, squamous cell carcinoma; *SCCis*, in situ squamous cell carcinoma.

to HCTZ (cumulative dose of >1500 DDU or 37,500 mg) showed a statistically significant association with invasive SCC, and a significant dose-response relationship was not detected. When stratified into subgroups by age and sex, HCTZ use was not significantly associated with invasive SCC, likely because the study was not sufficiently powered to detect these associations.

Interestingly, although the overall association between SCCis and HCTZ use was stronger than the association between invasive SCC and HCTZ, there was no association seen between the highest cumulative dosages of HCTZ (cumulative dose of >1500 DDU or >37,500 mg) and SCCis; however, both ever use and use of 500t o 1500 DDU of HCTZ were associated with SCCis development. It is possible that the study was not powered to identify associations of SCCis with different doses of HCTZ or that the observed relationship between ever use of HCTZ and SCCis was, in fact, spurious. When stratified by age and sex, HCTZ use was significantly associated with SCCis in male patients and individuals aged 50 years and older.

Previous studies evaluating the association of SCC with HCTZ use did not distinguish between cases of invasive SCC and SCCis, as noted earlier. The majority of these studies found a significantly increased risk of SCC with HCTZ use.[2] The 2 population-based studies found a significant dose-dependent increase in the risk

of cutaneous SCC and SCC of the lip in the Danish population.[1,4]

BCC

An association between BCC development and HCTZ use has been less consistently shown in previous research than the relationship between SCC and HCTZ,[2] possibly because BCCs have been shown to have longer promoter periods than SCC.[25] As a result of this longer promoter period, previous case-control studies evaluating the relationship of keratinocyte carcinoma with other exposures (eg, sunscreen) have frequently had more difficulty demonstrating an association with BCC than with SCC.

We found a significantly increased risk of BCC with HCTZ use with a clear dose-response relationship. The association was shown for ever users of HCTZ. When further stratified by cumulative dose, statistical significance was observed only at cumulative doses above 1500 DDU. These results may be explained by the fact that significantly longer periods of HCTZ use are required to observe an increased risk of BCC, as has been documented with other known causal exposures, or may suggest that this study was not powered to evaluate these smaller subgroups. Similarly, when divided into subgroups by age and sex, only people aged 50 years and older had a significant increase in BCC risk with HCTZ use.

Only 1 other population-based study, of the Danish population, evaluated the risk of BCC with HCTZ use.[1] The investigators identified a dose-dependent increase in BCC risk with use of HCTZ. Similarly, a cohort study from the United States showed a significant association between thiazides and increased BCC risk.[5] Two case-control studies from Denmark, a case-control multicenter study from Europe, and a cohort study from the Netherlands trended toward an association between BCC and thiazide use but did not reach statistical significance.[6,8,10,11] Of note, a recent meta-analysis that included all of the aforementioned studies found a marginal association between BCC development and HCTZ exposure.[2]

Strengths and limitations

An important strength of the study is the population-based design using record linkage of high-quality nationwide health registries. This design eliminates the drawbacks typical for most case-control studies, that is, a nonrepresentative control group and information bias. In addition, using the unique personal identification number for record linkage ensures accurate linkage and virtually no loss to follow-up. This study has several key limitations affecting its internal and external validity. The relationship between HCTZ and skin cancer raises the possibility of hypertension or other antihypertensive medications being possible confounders. Optimally, we would have included a control group on a separate antihypertensive medication, such as a beta-blocker or an angiotensin-converting enzyme inhibitor. However, we lacked sufficient power to assess this. Internal validity is primarily affected by the inherent limitations of the ICR. For example, the registry does not record potential confounders such as patient comorbidities, UV exposure habits, tanning bed use, smoking status, or socioeconomic status.[18] Finally, one possible explanation for the increased risk in HCTZ users could be the fact that they are under closer surveillance and, thus, are more frequently diagnosed with skin cancer, and this was impossible to correct for in this study.

CONCLUSION AND CLINICAL IMPLICATIONS

Our findings strengthen the argument that HCTZ exposure is associated with the development of SCCis, SCC, and BCC. This risk, at least for BCC and invasive SCC, was shown to be most pronounced in individuals with prolonged exposure to HCTZ. Importantly, a similar risk has not been observed with other Eighth Joint National Committee first-line antihypertensive medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers,[1,13] suggesting that a patient's individual skin cancer risk should be accounted for when choosing a first-line hypertensive. When HCTZ is initiated, patients should be counseled about the potential association of its use with keratinocyte carcinoma and, therefore, encouraged to practice sun protection. Because an association between keratinocyte carcinoma and HCTZ has now been documented in Iceland's low-UV environment, it is important to recognize that average sun protection behaviors may not necessarily eliminate the carcinogenic potential of HCTZ. Although additional studies are required to show that discontinuation of HCTZ decreases the risk of subsequent keratinocyte carcinoma development, the risk/benefit ratio of using HCTZ in patients at risk for keratinocyte carcinoma development needs to be carefully considered.

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