Hydrochlorothiazide increases risk of nonmelanoma skin cancer in an elderly Japanese cohort with hypertension: The Shizuoka study

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Background: Hydrochlorothiazide (HCT), a widely used hypertensive drug, has photocarcinogenic potential, leading to concerns about the development of nonmelanoma skin cancers (SCs) after intake. Despite substantial numbers of observational studies, the results remain inconsistent especially among Asian countries.

Objective: To assess the incidence of nonmelanoma SCs in hypertensive Japanese HCT users compared with nonusers.

Methods: A population-based, cohort nested, propensity score-matched study was conducted using the Shizuoka Kokuho database. All participants were patients aged ≥60 years. Hazard ratios for SC incidence were calculated in the matched cohorts using the propensity scores of potential confounders, sex, age category, comorbidities, and administration of methotrexate, cyclosporin, and statins.

Results: The risk of SC was higher in HCT users than in nonusers (hazard ratio, 1.58; 95% confidence interval, 1.04-2.40), with preferential sun-exposed location and a tendency to develop squamous cell carcinoma, but not basal cell carcinoma or Bowen disease.

Limitations: No additional information was available from other than medical records. The data were confined to a Japanese population.

Conclusion: HCT use increases the risk of SC in Japanese patients with hypertension and a dark skin type, highlighting the increased risk of SC among HCT users in the aging society worldwide. (JAAD Int 2023;12:49-57.)

Key words: big data; carcinogenesis; clinical research; cohort study; epidemiology; hydrochlorothiazide; observational study; skin cancer.

INTRODUCTION

Hypertension may cause life-threatening events.[1] It presents an increasing burden in elderly people[2] and is expected to expand rapidly worldwide in the next 2 decades. Cochrane analysis concluded that low-dose thiazides reduced all morbidity and mortality outcomes in adult hypertensive patients,[3] leading to the rapid spread of hydrochlorothiazide (HCT) use in many countries, including Japan. HCT is a well-known diuretic that is still used worldwide because of its safety, efficacy, and economic benefits.[1]

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In Japan, antihypertensives are used by 70% of older people and HCT is prescribed to 6.4% of them.[4] However, HCT is known to cause photosensitivity dermatitis[5,6] and also acts as a chromophore that absorbs UV radiation and transfers energy to adjacent pyrimidine nucleotides of DNA to form dimers with mutagenic potential.[7,8] Several epidemiologic studies accordingly warned that HCT use may be associated with a substantially increased risk of skin cancers (SCs),[9-31] leading to concern over the development of SCs after HCT intake. Recent meta-analyses indicated possible carcinogenesis in HCT users in non-Asian countries,[11,29,32] and in 2019, The International Agency for Research on Cancer claimed that HCT had carcinogenic potential as a class 2B agent.[33] However, conflicting results among Asian countries mean that its status remains debatable.[31,34-36] We aimed to clarify this issue in a population-based retrospective cohort study using the Shizuoka Kokuho database (SKDB), to improve our understanding of the potential cancer risks associated with HCT use in Japanese hypertensive patients.

CAPSULE SUMMARY

- Hydrochlorothiazide, a widely used drug, has demonstrated photocarcinogenic potential, leading to concerns about the development of nonmelanoma skin cancers in the users.
- Hydrochlorothiazide increases the risk of skin cancer even among Japanese hypertensive patients with relatively dark skin type, highlighting hazard of this usage in aging societies worldwide.

METHODS

Study design

This was a population-based, cohort nested, propensity score (PS)-matched study conducted using the SKDB. All participants were patients aged ≥60 years who were treated for hypertension during the study period. The primary outcome was the time to SC event onset, compared between HCT users and nonusers.

Setting and data source

Shizuoka prefecture was considered to be representative of Japan as a whole in terms of its population dynamics, nature, climate, industry, economy, and culture. The SKDB includes information on a regional, population-based longitudinal cohort comprising 2,230,848 Japanese individuals (women, n = 1,211,161; 54.3%) living in Shizuoka prefecture, near the center of Japan (population approximately 3.6 million),[37] and has been used as a data source in several studies.[38-41] Comprehensive personally linked data were collected and all individuals were assigned a unique identifier. The dataset includes basic information from the subscriber list (sex, age, zip code, observation period, and reason for disenrollment, including death). Claims data were obtained from public health insurance organizations (<75 years old, national health insurance; ≥75 years old, late-stage elderly medical care system [LSEMCS]). The SKDB is a suitable database for statistical studies in Japan because it contains accurate information on deaths and losses to follow-up from Japan's Basic Resident Registration Network System. Furthermore, the database uses the *International Classification of Diseases, 10th Revision* (ICD-10) codes to search and classify diagnoses.

Study population

We conducted a database-nested cohort study using the SKDB during a study period from April 1, 2012, to September 30, 2020. All participants were aged ≥60 years and subscribed to national health insurance or LSEMCS during the study period. Cohort entry was defined as the registration date with the respective health insurance agency or April 1, 2012, whichever occurred later. The exclusion assessment window was from 1 year before the index date. Patients already prescribed HCT, patients diagnosed with nonmelanoma SC including solar keratosis (squamous cell carcinoma [SCC] in situ of skin), lymphoma, AIDS, and metastatic solid tumors, and patients who were not prescribed hypertension medication were excluded.

Baseline conditions

The covariate assessment window was from 1 year before the index date. Comorbidities were examined using the Charlson/Elixhauser comorbidy indexes.[42] Related confounders were age, sex, Charlson and Elixhauser comorbidities, and use of drugs that might impact cancer development, including cyclosporin-A, methotrexate, and statins.[43-45] The participants were categorized into 4 age groups (60-69 years, 70-79 years, 80-89 years, and ≥90 years) and according to the presence or absence of comorbidities and drug use.

HCT and SC incidence

The primary outcome was time to SC event onset, including SCC in situ, such as solar keratosis and Bowen disease. An SC event was defined using

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
HCT:	hydrochlorothiazide
HR:	hazard ratio
ICD-10:	International Classification of Diseases, 10th Revision
LSEMCS:	late-stage elderly medical care system
PS:	propensity score
SCC:	squamous cell carcinoma
SCs:	skin cancers
SKDB:	Shizuoka Kokuho database

ICD-10[46] (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/2sn9k5g3n7/1). We used a new-user design to estimate the causal effect of HCT exposure on SC incidence with less bias.[47] The index date was defined as the day on which HCT was first prescribed for patients in the HCT-user group and as the day of 1 year after cohort entry date in the non-HCT user group. We adopted a 1-year latency period between the index date and SC onset in the HCT user and non-HCT user groups, consistent with a similar study[48] and primary cutaneous cancer doubling times.[49] The end date of the follow-up period was defined as the date of SC development, the end date of the study (September 30, 2020), or the withdrawal date from the national health insurance or LSEMCS program, whichever occurred first.

Statistical analyses

Means and interquartile ranges were calculated for continuous variables and frequencies (percentage) for categorical variables for both groups. Missing values were not imputed. Individual PSs for HCT exposure as an outcome variable were estimated using a multivariate logistic regression model conditional on potential confounders. One-to-one greedy matching was implemented with a caliper width equal to 0.20 of the standard deviation of the logit of the PS. Standardized mean differences with a cutoff value of 0.10 were then adopted to assess the balance of covariates between the 2 groups in the overall population and the PS-matched population. Hazard ratios (HRs) and the 95% confidence intervals (CIs) for the risk of SC development were estimated using a univariate Cox proportional hazards regression model.

Sensitivity analysis was conducted to evaluate the relationship between HCT, as a potential photocarcinogen, and the incidence of SC in sun-exposed areas. However, detailed data on the location of SC were not available in the SKDB, and we therefore, designated the face, neck, hands, and forearms as sun-exposed sites and other sites as sun-unexposed sites. We then compared the risk of SC between the HCT user and non-HCT user cohorts matched for PSs. This study did not assess the relationship between cumulative HCT dose and SC development because of the difficulty in acquiring the data. We also conducted an additional analysis to investigate the pathological types of SC associated with HCT administration, although relevant data were similarly only available for limited cases from the SKDB.

All statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc.). All measures of associations were reported with the corresponding 95% CIs. All statistical tests were two-sided. CIs not overlapping 1.0 indicated statistical significance.

Ethics and data availability statements

The SKDB data were anonymized.[37] The study protocol was approved by the ethics committee of Shizuoka Graduate University of Public Health (#SGUPH_2021_001_028), and the study was conducted according to the REporting of studies Conducted using Observational Routinely-collected Health Data (RECORD) reporting guidelines.[50] These data are administrated by the Shizuoka prefectural government and access is regulated to protect personal information. The data are only available to researchers after obtaining the appropriate permissions.

RESULTS

Study cohort

A flowchart showing the cohort selection and construction of the study cohorts is shown in Fig 1. The source cohort consisted of 2,230,848 participants. The unmatched baseline characteristics after applying the respective exclusion criteria and exposure definitions are shown in Table I. Of 459,097 hypertensive patients treated with drugs, 12,219 (2.7%) patients received medication containing HCT and 446,878 (97.3%) patients received non-HCT drugs. Compared with non-HCT users, HCT users tended to be older (>70 years, $P < .001$) and predominantly male ($P < .001$). There was a significant difference in the cumulative incidence of SC between the HCT user (46/12,219, 0.4%) and non-HCT user groups (2476/446,876, 0.6%) during a follow-up period of 7.5 years (median, 7.12 years; max 7.5 years, 2,571,073.00 person-years) (odds ratio, 0.68; $P = .01$).

Skin cancers

Because of diversity in the baseline covariates between the groups, 12,197 patients from each group (HCT users and non-HCT users) were

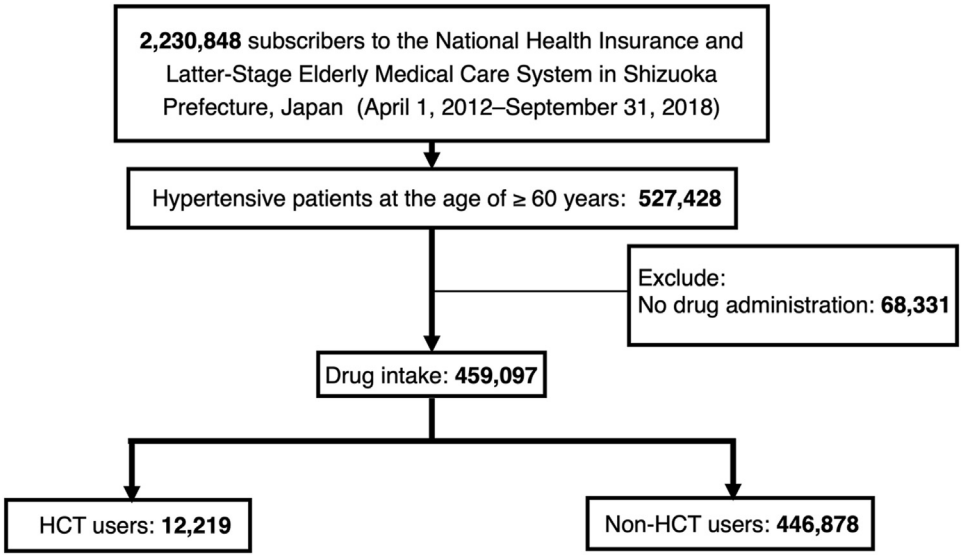

Fig 1. Flow diagram of study participants. *HCT*, Hydrochlorothiazide.

matched in a 1:1 ratio using propensity score estimation/matching and were then compared using a Cox proportional hazards regression model. The baseline characteristics of the matched cohorts for the primary outcome indicated that they were well-balanced (standardized differences <10%) (Tables I and II).

The proportional hazards assumption was fulfilled. After matching propensity scores, SC occurred in 46 of 12,197 HCT users (expected 36.0 patients) (5-year incidence, 0.47%; 95% CI, 0.39%-0.55%) compared with 47 of 12,197 nonusers (expected 57.0 patients) (5-year incidence, 0.36%; 95% CI, 0.30%-0.42%). The difference was significant according to log-rank test (P = .03) and Cox hazard analysis (HR, 1.58; 95% CI, 1.04-2.40) (Fig 2).

Sensitivity analysis

Because sun exposure could be critical to the induction of SC in HCT users, we further investigated if SCs in HCT users arose preferentially in sun-exposed areas. Data on the SC location was available for 2522 cases (79.9%) in the database (1457 cases in sun-exposed areas and 558 cases in sun-unexposed areas). SCs without location records were postulated to arise at unknown locations. A Cox proportional hazard regression model adjusted by covariates of age, sex, comorbidities, and drugs, including cyclosporin, methotrexate, and statins, using PS-matched groups showed an increase in the risk of SC in sun-exposed areas (HR, 2.29; 95% CI, 1.35-3.88; log-rank test P = .0022) (Supplementary Table IA, available via Mendeley at xxx) in HCT users compared with nonusers. The incidence of SC in sun-unexposed areas was comparable between the groups (HR, 1.21; 95% CI, 0.47-3.08; P = .70) (Supplementary Table IB, available via Mendeley at xxx). These results support the primary analysis.

Additional analysis

SC comprises various pathological types with different origins and etiologies. We further investigated which pathological types of SC were associated with HCT use. Recorded pathological data were available for 1657 SC cases (65.7%). Basal cell carcinoma (BCC) was the most frequent type (28.9%, 726 cases), followed by SCC (23.1%, 583 cases), and Bowen disease (9.1%, 229 cases). Other types of SC were not analyzed because of insufficient numbers. SCs lacking pathology records were postulated to be SCs of unknown pathology. We found a 4.99-fold increase in risk of SCC (HR, 4.99; 95% CI, 2.00-12.52) (Supplementary Table IIA, available via Mendeley at xxx) in HCT users compared with nonusers, but no increased risk of BCC (HR, 1.35; 95% CI, 0.65-2.79) (Supplementary Table IIB, available via Mendeley at xxx) or Bowen disease (HR, 1.21; 95% CI, 0.39-3.76) (Supplementary Table IIC, available via Mendeley at xxx).

DISCUSSION

The results of this study demonstrated that HCT promoted the development of SC in elderly Japanese patients with hypertension. To the best of our knowledge, this was the first regional-based

Table I. Demographic profiles

Variable	Category	HCT treatment		SMD
		No (%)	Yes (%)	
		446,878 (97.3)	12,219 (2.7)	
Age (years, SD)		78.11 (9.33)	77.63 (8.36)	0.055
Age	60 to <70 y	96,902 (21.7)	2431 (19.9)	0.190
	70 to <80 y	154,219 (34.5)	4566 (37.4)	
	80 to <90 y	138,763 (31.1)	4300 (35.2)	
	90 y and above	56,994 (12.8)	922 (7.5)	
Sex	Men	192,702 (43.1)	4908 (40.2)	0.060
	Women	254,176 (56.9)	7311 (59.8)	
Comorbidities				
Cerebrovascular disease	Presence	122,066 (27.3)	3565 (29.2)	0.041
Dementia	Presence	28,536 (6.4)	1127 (9.2)	0.106
Myocardial infarction	Presence	18,967 (4.2)	366 (3.0)	0.067
Renal disease	Presence	26,349 (5.9)	755 (6.2)	0.012
Congestive heart failure	Presence	94,890 (21.2)	3087 (25.3)	0.096
Peripheral vascular disease	Presence	66,871 (15.0)	2075 (17.0)	0.055
Chronic pulmonary disease	Presence	103,327 (23.1)	3009 (24.6)	0.035
Rheumatic disease	Presence	15,651 (3.5)	442 (3.6)	0.006
Peptic ulcer disease	Presence	98,530 (22.0)	2392 (19.6)	0.061
Mild liver disease	Presence	82,344 (18.4)	2152 (17.6)	0.021
Diabetes without chronic complication	Presence	12,359 (2.8)	349 (2.9)	0.005
Diabetes with chronic complication	Presence	37,977 (8.5)	1097 (9.0)	0.017
Hemiplegia or paraplegia	Presence	8223 (1.8)	183 (1.5)	0.027
Moderate or severe liver disease	Presence	1338 (0.3)	25 (0.2)	0.019
Cardiac arrhythmias	Presence	88,449 (19.8)	2343 (19.2)	0.016
Vulvar disease	Presence	33,734 (7.5)	935 (7.7)	0.004
Pulmonary circulation disorders	Presence	1590 (0.4)	37 (0.3)	0.009
Hypertension, uncomplicated	Presence	445,269 (99.6)	12,189 (99.8)	0.021
Other neurological disorders	Presence	20,891 (4.7)	591 (4.8)	0.008
Diabetes, uncomplicated	Presence	11,174 (2.5)	313 (2.6)	0.004
Diabetes, complicated	Presence	38,435 (8.6)	1108 (9.1)	0.016
Hypothyroidism	Presence	10,815 (2.4)	353 (2.9)	0.029
Renal failure	Presence	26,317 (5.9)	753 (6.2)	0.011
Liver disease	Presence	82,619 (18.5)	2159 (17.7)	0.021
Peptic ulcer disease excluding bleeding	Presence	96,758 (21.7)	2337 (19.1)	0.063
Rheumatoid arthritis/collagen vascular diseases	Presence	18,990 (4.2)	533 (4.4)	0.006
Coagulopathy	Presence	4979 (1.1)	155 (1.3)	0.014
Obesity	Presence	2109 (0.5)	76 (0.6)	0.020
Weight loss	Presence	1725 (0.4)	74 (0.6)	0.031
Fluid and electrolyte disorders	Presence	54,447 (12.2)	1624 (13.3)	0.033
Blood loss anemia	Presence	1119 (0.3)	41 (0.3)	0.016
Deficiency anemia	Presence	41,897 (9.4)	1296 (10.6)	0.041
Alcohol abuse	Presence	3070 (0.7)	83 (0.7)	0.001
Drug abuse	Presence	96 (0.0)	4 (0.0)	0.007
Depression	Presence	28,994 (6.5)	1000 (8.2)	0.065
Psychoses	Presence	9055 (2.0)	308 (2.5)	0.033
Medicine				
Ciclosporin	Taken	595 (0.1)	14 (0.1)	0.005
Methotrexate	Taken	3244 (0.7)	69 (0.6)	0.020
Statins	Taken	446,878 (100.0)	12,197 (99.8)	0.060
Skin cancers	Taken	2476 (0.6)	46 (0.4)	0.026

HCT, Hydrochlorothiazide; *SMD*, standardized mean difference

Table II. Demographics of matched cohorts

		HCT treatment		
		No (%)	Yes (%)	
Variable	Category	12,197	12,197	SMD
Age (years, SD)		77.68 (8.54)	77.63 (8.36)	0.006
Age	60 to <70 y	2440 (20.0)	2423 (19.9)	0.009
	70 to <80 y	4523 (37.1)	4562 (37.4)	
	80 to <90 y	4291 (35.2)	4293 (35.2)	
	90 y and above	943 (7.7)	919 (7.5)	
Sex	Men	4908 (40.2)	4901 (40.2)	0.001
	Women	7289 (59.8)	7296 (59.8)	
Comorbidities				
Cerebrovascular disease	Presence	3490 (28.6)	3559 (29.2)	0.012
Dementia	Presence	1104 (9.1)	1123 (9.2)	0.005
Myocardial infarction	Presence	323 (2.6)	365 (3.0)	0.021
Renal disease	Presence	688 (5.6)	754 (6.2)	0.023
Congestive heart failure	Presence	3123 (25.6)	3084 (25.3)	0.007
Peripheral vascular disease	Presence	2068 (17.0)	2074 (17.0)	0.001
Chronic pulmonary disease	Presence	2996 (24.6)	3007 (24.7)	0.002
Rheumatic disease	Presence	413 (3.4)	442 (3.6)	0.013
Peptic ulcer disease	Presence	2398 (19.7)	2392 (19.6)	0.001
Mild liver disease	Presence	2068 (17.0)	2151 (17.6)	0.018
Diabetes without chronic complication	Presence	301 (2.5)	349 (2.9)	0.024
Diabetes with chronic complication	Presence	1100 (9.0)	1097 (9.0)	0.001
Hemiplegia or paraplegia	Presence	163 (1.3)	183 (1.5)	0.014
Moderate or severe liver disease	Presence	17 (0.1)	25 (0.2)	0.016
Cardiac arrhythmias	Presence	2311 (18.9)	2342 (19.2)	0.006
Vulvar disease	Presence	891 (7.3)	934 (7.7)	0.013
Pulmonary circulation disorders	Presence	29 (0.2)	37 (0.3)	0.013
Hypertension, uncomplicated	Presence	12,172 (99.8)	12,167 (99.8)	0.009
Other neurological disorders	Presence	539 (4.4)	590 (4.8)	0.02
Diabetes, uncomplicated	Presence	268 (2.2)	313 (2.6)	0.024
Diabetes, complicated	Presence	1108 (9.1)	1108 (9.1)	<0.001
Hypothyroidism	Presence	323 (2.6)	353 (2.9)	0.015
Renal failure	Presence	686 (5.6)	752 (6.2)	0.023
Liver disease	Presence	2072 (17.0)	2158 (17.7)	0.019
Peptic ulcer disease excluding bleeding	Presence	2350 (19.3)	2337 (19.2)	0.003
Rheumatoid arthritis/collagen vascular diseases	Presence	506 (4.1)	533 (4.4)	0.011
Coagulopathy	Presence	150 (1.2)	155 (1.3)	0.004
Obesity	Presence	66 (0.5)	75 (0.6)	0.01
Weight loss	Presence	64 (0.5)	74 (0.6)	0.011
Fluid and electrolyte disorders	Presence	1574 (12.9)	1624 (13.3)	0.012
Blood loss anemia	Presence	26 (0.2)	41 (0.3)	0.024
Deficiency anemia	Presence	1289 (10.6)	1292 (10.6)	0.001
Alcohol abuse	Presence	68 (0.6)	83 (0.7)	0.016
Drug abuse	Presence	4 (0.0)	4 (0.0)	<0.001
Depression	Presence	943 (7.7)	1000 (8.2)	0.017
Psychoses	Presence	293 (2.4)	308 (2.5)	0.008
Medicine				
Ciclosporin	Taken	8 (0.1)	14 (0.1)	0.016
Methotrexate	Taken	58 (0.5)	69 (0.6)	0.013
Statins	Taken	12,197 (100.0)	12,197 (100.0)	<0.001

HCT, Hydrochlorothiazide; *SMD*, standardized mean difference.

population retrospective cohort study in Japan using PS-matched cohorts adjusted for covariates of age, sex, major comorbid disease categories, and drugs influencing SC development. There is currently controversy regarding the effects of HCT on the development of SC in Asian, but not non-Asian

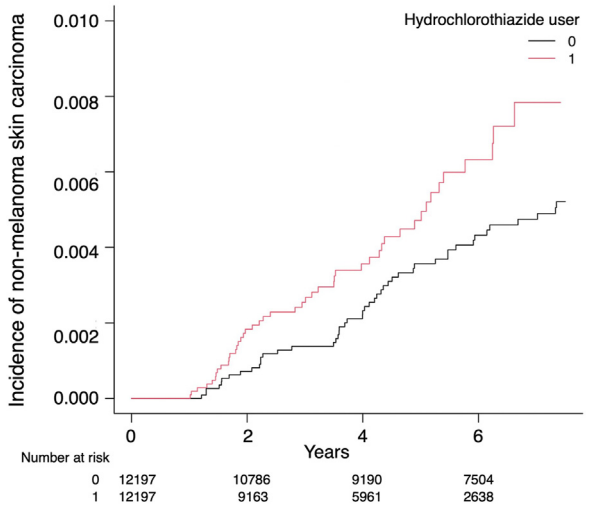

Fig 2. Cumulative incident curve of skin cancers in hypertension patients treated with and without hydrochlorothiazide.

patients, with some studies indicating an increased risk,[18] inconclusive evidence,[34,35] or a protective role[36] for SC development. Although one cohort study[36] was postulated to have an immortal time bias,[51] we considered that the conflict might be derived from differences in the covariates selected for adjustment among the studies, such as comorbid disease categories, because unbalanced covariates will lead to an incorrect interpretation of the results and conflicting conclusions. In contrast to the PS-matched analysis in this study, the unmatched cohorts showed a marked deviation in case numbers (19/36) of comorbid disease categories between HCT and non-HCT users ($P < .05$, χ^2 analysis), and simple analysis demonstrated no effect of HCT on the incidence of SC. This suggests that some comorbid disease categories might become confounders, and appropriate adjustment of covariates is thus crucial to detect a robust effect of HCT on SC development, as shown in this study. Although it would be preferable to analyze the relationship between the cumulative HCT dose and SC incidence, most Japanese hypertensive patients take 12.5 mg/day of HCT, and the cumulative dose thus increases in proportion to the duration of administration, and we therefore, did not carry out this analysis in the current study.

Asians, including Japanese, with dark skin phototypes III to V are relatively resistant to UV-induced oncogenesis.[52] However, the current results indicated that HCT increased the risk of SC in sun-exposed sites even in Japanese patients, as in Caucasians,[11] implicating the potential photocarcinogenic effect of HCT in a wider regional setting. Furthermore, this effect was closely associated with the emergence of SCC but not BCC or Bowen disease, as shown in a previous report.[28] Although the reason for this difference remains unclear, it might reflect different origins and etiologies. SCC originates from keratinocytes in the upper level of the skin, to which UV can penetrate quickly. However, it remains unclear why BCC, as the most common SC in sun-exposed areas,[53] was unaffected by HCT intake. Notably, intermittent, intense sun exposure carries a high risk for the development of BCC, while SCC is strongly associated with lower level chronic exposure,[54] suggesting that the pathology is affected by the quality of UV radiation, which might thus also be associated with the development of HCT-associated SC. The etiology of Bowen disease is accepted to be multifactorial, in association with not only sun exposure but also arsenic exposure and human papilloma virus infection.[55,56] This result is consistent with the HCT-modified UV action in SC development. Further investigations are thus needed to clarify photoprotection measures and the avoidance of HCT use to prevent SC development in such populations, as suggested previously.[25]

Strengths and limitations

The main strength of this study was the use of matched cohorts from a database that allowed long-term follow-up of up to 7.5 years and captured a clear outcome, that is, the development of SC. However, this study also had several limitations because all the data were derived from the SKDB. First, we could not obtain additional information about the SCs, patients' occupations, duration of exposure to sunlight, compliance with drug administration, exact cumulative drug dose, or the severity of comorbidities. Second, diagnoses were defined using only ICD-10 codes in the medical records. Third, genetic predisposition factors were not incorporated.

CONCLUSION

This population-based cohort study showed that long-term use of low-dose HCT increases the risk of SC in Japanese patients with hypertension, including individuals with relatively dark skin. This was demonstrated by a significant increase in the incidence of sun-exposure–related SC and the preferential development of SCC in HCT users. These results highlight the increasing risk of SC associated with increased HCT use in aging societies worldwide.

Conflicts of interest

None disclosed.

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