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Use of hydrochlorothiazide and risk of skin cancer in a large nested case-control study in Spain

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Abstract

Purpose: Hydrochlorothiazide (HCTZ) use has been linked to skin cancer in northern European countries. We assessed the association between HCTZ exposure and risk of malignant melanoma (MM) and keratinocyte carcinoma (KC) in a European Mediterranean population.

Methods: Two parallel nested case-control studies were conducted in Spain using two electronic primary healthcare databases, each one providing data on both exposure and outcomes: SIDIAP and BIFAP. Cancer cases were matched to 10 controls by age and gender through risk-set sampling. The ORs and 95% CI for MM and KC associated with previous HCTZ use were estimated using conditional logistic regression. In BIFAP, KC cases were further identified as basal cell carcinoma (BCC) or squamous cell carcinoma (SCC).

Results: In adjusted analyses, both ever and cumulative high (≥50,000 mg) use of HCTZ were associated with an increased risk of KC. The risk estimates for high use were 1.30 (1.26–1.34) in SIDIAP and 1.20 (1.12–1.30) in BIFAP, with a lower risk for BCC (1.11 [1.02–1.21]) than for SCC (1.71 [1.45–2.02]). A dose–response relationship was observed between cumulative doses of HCTZ and KC risk. Inconsistent results were found for high use of HCTZ and risk of MM: 1.25 (1.09–1.43) in SIDIAP and 0.85 (0.64–1.13) in BIFAP.

Conclusions: In this European Mediterranean population, a high cumulative use of HCTZ was related to an increased risk of KC with a clear dose–response pattern.

KEYWORDS
case-control, HCTZ, keratinocyte carcinoma, malignant melanoma, pharmacoepidemiology

Key Points

- The relationship between hydrochlorothiazide use and the risk of developing skin cancer has not been specifically evaluated in European Mediterranean populations.

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers; BCC, Basal cell carcinoma; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CCB, Calcium-channel blockers; CCI, Charlson Comorbidity Index; CI, Confidence interval; DDD, Defined daily doses; HCTZ, Hydrochlorothiazide; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; IDIAPJGol, Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina; IR, Incident Rate; IRR, Incidence Rate Ratio; KC, Keratinocyte carcinoma; MM, Malignant melanoma; NSAID, Non-steroidal antiinflammatory drugs; OR, Odds ratio; PPV, Positive Predictive Value; SCC, Squamous cell carcinoma; SIDIAP, The Information System for Research in Primary Care; UK, United Kingdom; UV, Ultraviolet.

The authors declare this paper is original and has not been previously submitted for review to any other journal.

- In this large nested case-control study conducted in Spain, a high cumulative use of hydrochlorothiazide was related to an increased risk of keratinocyte carcinoma, with a clear dose–response pattern.
- A high cumulative use of hydrochlorothiazide was related to a higher relative risk of squamous cell carcinoma than basal cell carcinoma.
- Inconsistent results between both databases were found for high use of hydrochlorothiazide and risk of malignant melanoma.

1 | INTRODUCTION

The use of antihypertensive and diuretic drugs has been previously associated with an increased risk of skin cancer.[1–6] However, most findings were not directly comparable mainly due to differences in the study methods used and study-specific limitations. Recently, several studies have found an increased risk of skin and lip cancer related to high cumulative doses of hydrochlorothiazide (HCTZ) in populations from Denmark,[7–9] Iceland,[10] United Kindom[11–13] and Australia,[14] but not in a population from Taiwan.[15]

The relationship between HCTZ and skin cancer may be partly explained by the photosensitivity of HCTZ,[16,17] due to the interaction between the chemical structure of this drug and ultraviolet (UV) radiation. There are several risk factors for developing skin cancer, including genetic characteristics as well as sun exposure.[18–20] It is therefore of relevance to study this association in different populations with variable characteristics in terms of sun exposure and UV skin susceptibility.

We conducted a study examining the relationship between HCTZ use and the risk of developing malignant melanoma (MM) and keratinocyte carcinoma (KC), including subtypes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), in Spain, a European Mediterranean population, using two different databases of electronic health records from primary care.

2 | PATIENTS AND METHODS

2.1 | Data sources

The present study was performed using two large prospective population-based databases from Spain: SIDIAP (the Information System for Research in Primary Care; www.sidiap.org),[21] and BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; www.bifap.org).[22] Briefly, both contain information recorded in anonymized patients' electronic health records collected prospectively by health professionals in Spain during routine visits in primary care. Data include clinical diagnoses coded with the International Classification of Diseases 9th and 10th revisions (ICD-9, ICD-10) and the International Classification of Primary Care (ICPC-2), and information on drugs prescribed in primary care or dispensed in community pharmacies. SIDIAP includes registries for nearly 6 million people since 2005 in the Catalonia region. BIFAP contains information on 12 million patients from different Spanish regions since 2001.

2.2 | Study design and population

For each database, a case–control design nested in a cohort during 2007–2017 was performed. Patients aged ≥18 years entered the cohort once registered with a Primary Care Physician for at least 2 years. The study cohort was followed until the earliest occurrence of an incident MM or KC (BCC or SCC) (index date), death, any exclusion criteria was met, the patient left the practice, the practice left the database (in BIFAP only) or end of the study period. Patients were free of the following exclusion criteria at index date and during follow-up: any cancer diagnosis and any of the following immunosuppressive disease or immunosuppressant therapy (as they may induce skin cancer)[23,24]: organ transplantation, HIV diagnosis, use of azathioprine, cyclosporin, or mycophenolate mofetil. The flow chart of the study is available in Figure 1.

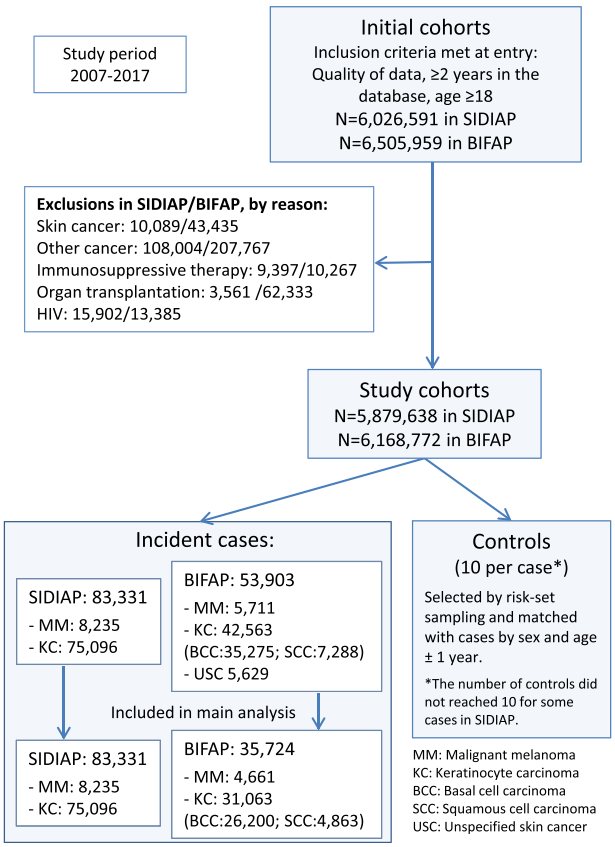

FIGURE 1 Flowchart for HCTZ and skin cancer [Colour figure can be viewed at wileyonlinelibrary.com]

2.3 | Case identification and validation

Diagnoses of skin cancer were identified using ICPC-2, ICD-9 and ICD-10 codes (see Appendix, Supplementary Information). In BIFAP, a double and independent validation process was carried out using a specific algorithm and a natural language processing procedure. Both approaches took into account comments in free text, when found in patient records, to validate the potential cases that had been automatically captured by skin cancer codes. In SIDIAP, a subsample of cancer cases was previously validated through linkage to two regional population-based cancer registries in Catalonia.[25]

2.4 | Selection of controls

For each case, up to 10 controls were randomly selected from the pool of eligible person-time (risk-set sampling) (Figure 1). Controls were matched to cases by sex and age ± 1 year. The index date for each control was the MM and KC date of the matched case. Subjects were eligible for sampling as controls one or more times before possibly becoming cases.

2.5 | Exposure definition

HCTZ use definition was based on pharmacy dispensing in SIDIAP and in prescription/dispensing in BIFAP.

HCTZ was considered alone or in combination with other active substances (see ATC codes in Appendix, Supplementary Information). Exposures in the 2 years before the index date were excluded from all analyses and exposure definitions.

Exposure windows were defined as never use (reference category): no HCTZ-containing drug before the index date; and ever use: having filled at least one prescription any time before the index date. Cumulative exposure was calculated by adding the total number of doses for the total number of prescriptions/dispensing. In BIFAP, such calculation takes into account the duration of the prescription according to the physician instructions. The following categories for dose were explored: 1–9999 mg, 10 000–24 999 mg, 25 000–49 999 mg, 50 000–74 999 mg, 75 000–99 999 mg, 100 000–149 999 mg, 150 000–199 999 mg, and ≥ 200 000 mg. High use was defined as ≥50 000 mg of HCTZ as suggested previously[8] and corresponding to approximately 6 years of cumulative use, representing 2000 defined daily doses (DDD).[26]

2.6 | Other analytical variables

Potential confounders included: a) total follow-up time registered in the database; b) use of selected drugs with suggested photosensitizing properties (oral retinoids, topical retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, and methoxypsoralene[27–30]), or suggested anti-neoplastic effects (aspirin, other non-steroidal antiinflammatory drugs, statins[31]); and use of corticosteroids; c) Charlson Comorbidity Index (CCI) scores in SIDIAP (0: low; 1–2: medium; >2: high); or the following comorbidities in BIFAP, as CCI was not available in this database: diabetes, chronic obstructive pulmonary disease, myocardial infarction, heart failure, peripheral vascular disease, stroke, chronic renal insufficiency, dementia or Alzheimer disease, connective tissue disease, gastric ulcer, hemiplegia, and hepatic disease; d) smoking status (non-smokers; current/former smokers).

Exposure to each potential confounder drug was defined as two or more prescriptions on separate dates. For all covariates, information within 2 years prior to the index date was disregarded.

Additional potential confounding that may derive from different levels of completeness or exhaustiveness between both databases was further considered in sensitivity analyses.

2.7 | Statistical analysis

All the analyses were performed locally and estimates are provided by database.

Incident Rate (IR) by 100 000 persons-years was calculated for each type of cancer. Odds ratio (OR) and 95% confidence interval (95% CI) were computed from conditional logistic regression models, which under the assumption of the incidence density matching approach represent Incidence Rate Ratios (IRR). Estimates were adjusted for pre-selected confounders specified above. In BIFAP, additional IRR were calculated separately for BCC and SCC. In ever users, we stratified analyses according to specific categories of cumulative HCTZ use, in which the effect of dose–response was explored by estimating the incremental OR for each 10 000 mg of HCTZ using unconditional regression adjusted by age (continuous) and sex. The association was also examined stratifying by the following population subgroups: sex, age, never-user of drugs with suggested photosensitizing properties, no diabetics, with low comorbidity (CCI = 0 in SIDIAP and none of the chronic diseases considered in BIFAP), with no history of actinic keratosis (associated with UV-exposure and considered a precursor of KC[32]), and no history of atopic dermatitis and psoriasis (associated to UV-exposure and possibly associated with KC risk[33,34]). Absolute risks with high use of HCTZ were estimated by IR* (IRR-1) and they were used to calculate the number of patients needed to be exposed to cause one additional case per year.

2.7.1 | Sensitivity and secondary pre-specified analyses

To assess the impact of differences in methods with previous studies and between the two Spanish databases, four sensitivity analyses were performed. In BIFAP, an additional and broader case definition was considered, including all recorded skin cancer cases identified by

TABLE 1 Characteristics of skin cancer cases and matched controls by cancer subtype and data source

	SIDIAP Malignant melanoma		SIDIAP Keratinocyte carcinoma		BIFAP Malignant melanoma		BIFAP Keratinocyte carcinoma	
Subgroup	Cases $N = 8235$	Controls $N = 79\,843$	Cases $N = 75\,096$	Controls $N = 739\,004$	Cases $N = 4661$	Controls $N = 46\,610$	Cases $N = 31\,063$	Controls $N = 310\,630$
Age, median (interquartile range)	60 (46–72)	61 (47–73)	74 (63–82)	74 (63–82)	61 (48–73)	61 (48–73)	73 (63–82)	73 (63–82)
Sex, male	3622 (43.7)	35 275 (43.8)	35 228 (46.5)	347 229 (46.7)	2058 (44.2)	20 580 (44.2)	15 025 (48.4)	150 250 (48.4)
Use of HCTZ								
Never use	6458 (78.4)	64 514 (80.8)	48 470 (64.5)	507 529 (68.7)	3910 (83.9)	40 224 (86.3)	23 581 (75.9)	246 446 (79.3)
Ever use	1777 (21.6)	15 329 (19.2)	26 626 (35.5)	231 475 (31.3)	751 (16.1)	6386 (13.7)	7482 (24.1)	64 184 (20.7)
High use	268 (3.30)	2250 (2.8)	5421 (7.2)	41 362 (5.6)	55 (1.2)	510 (1.1)	871 (2.8)	5372 (1.7)
Ever use of photosensitizing drugs								
Topical retinoids	0 (0)	0(0)	0 (0)	0(0)	0 (0)	0 (0)	2 (0.01)	13 (0)
Oral retinoids	14 (0.2)	84 (0.1)	71 (0.1)	500 (0.1)	3 (0.1)	20 (0.0)	12 (0.00)	75 (0.0)
Tetracycline	6 (0.1)	35 (0.0)	43 (0.1)	343 (0.1)	0 (0)	14 (0.0)	12 (0.0)	61 (0.0)
Macrolides	587 (7.1)	5301 (6.6)	7992 (10.6)	66 107 (9.0)	500 (10.7)	4105 (8.8)	3941 (12.7)	29 882 (9.6)
Aminoquinolines	19 (0.2)	162 (0.2)	216 (0.3)	1806 (0.2)	7 (0.2)	89 (0.2)	87 (0.3)	630 (0.2)
Amiodarone	75 (0.9)	641 (0.8)	1450 (1.9)	12 419 (1.7)	47 (1.0)	325 (0.7)	464 (1.5)	3528 (1.1)
Metoxypsoralene	1 (0.0)	4 (0.0)	9 (0.0)	76 (0.0)	0 (0)	7 (0.0)	5 (0.0)	26 (0.0)
Other drugs use								
Aspirin	1026 (12.5)	9357 (11.7)	17 231 (22.9)	154 710 (20.9)	534 (11.5)	4957 (10.6)	5843 (18.8)	52 608 (16.9)
No-aspirin NSAID	3740 (45.4)	35 122 (44.0)	43 824 (58.4)	386 219 (52.3)	2354 (50.5)	20 932 (44.9)	16 807 (54.1)	141 560 (45.6)
Statins	1957 (23.8)	17 393 (21.8)	27 655 (36.8)	248 957 (33.7)	1057 (22.7)	9487 (20.4)	9818 (31.6)	87 152 (28.1)
Glucocorticoids	381 (4.6)	3770 (4.7)	6431 (8.6)	55 322 (7.5)	242 (5.2)	2131 (4.6)	2403 (7.7)	19 105 (6.2)
Charlson index (in SIDIAP) or number of diagnoses[a] (in BIFAP)								
0	7275 (88.3)	70 216 (87.9)	65 540 (87.3)	645 890 (87.4)	3414 (73.3)	34 286 (73.6)	18 968 (61.1)	195 669 (63.0)
1–2	779 (9.5)	7958 (10.0)	7710 (10.3)	75 401 (10.2)	1176 (25.2)	11 576 (24.8)	11 151 (35.9)	106 425 (34.3)
>2	181 (2.2)	1669 (2.1)	1846 (2.4)	17 713 (2.4)	71 (1.5)	748 (1.6)	944 (3.0)	8536 (2.7)
Diabetes	1003 (12.20)	10 047 (12.60)	15 139 (20.20)	144 314 (19.50)	552 (11.84)	5362 (11.50)	5124 (16.50)	50 752 (16.34)
Smoking (current and former)	1254 (15.2)	13 037 (16.3)	9221 (12.3)	86 943 (11.8)	998 (21.4)	8967 (19.2)	6088 (19.6)	52 212 (16.8)
Use of other diuretics/antihypertensive drugs								
Furosemide	296 (3.6)	2698 (3.4)	6084 (8.1)	52 353 (7.1)	211 (4.5)	2106 (4.5)	2658 (8.6)	25 425 (8.2)
Calcium Channel Blockers	685 (8.3)	5785 (7.3)	11 336 (15.1)	98 259 (13.3)	494 (10.6)	4213 (9.0)	5237 (16.9)	43 798 (14.1)

TABLE 1 (Continued)

Subgroup	SIDIAP Malignant melanoma		SIDIAP Keratinocyte carcinoma		BIFAP Malignant melanoma		BIFAP Keratinocyte carcinoma	
	Cases $N = 8235$	Controls $N = 79\,843$	Cases $N = 75\,096$	Controls $N = 739\,004$	Cases $N = 4661$	Controls $N = 46\,610$	Cases $N = 31\,063$	Controls $N = 310\,630$
ACE inhibitors	1594 (19.4)	14 787 (18.5)	24 639 (32.8)	223 582 (30.3)	838 (18.0)	7648 (16.4)	8480 (27.3)	75 384 (24.3)
Angiotensin receptor blockers	1157 (14.0)	9246 (11.6)	16 263 (21.7)	144 137 (20.0)	761 (16.3)	6288 (13.5)	7125 (22.9)	64 192 (20.7)
Indapamide	209 (2.5)	1631 (2.1)	3078 (4.1)	26 111 (3.5)	137 (2.9)	1116 (2.4)	1399 (4.5)	11 652 (3.8)
Amiloride	116 (1.4)	998 (1.3)	2132 (2.8)	16 115 (2.2)	134 (2.9)	1193 (2.6)	1626 (5.2)	12 368 (4.0)
Follow-up in years, median (interquartile range)	6.96 (4.41–9.45)	6.95 (4.43–9.42)	7.94 (5.43–10.00)	7.94 (5.43–10.00)	6.4 (4.3–9.4)	5.6 (3.7–8.2)	6.6 (4.5–9.7)	5.6 (3.8–8.2)

Note: Data are presented as n (%) unless otherwise noted. ACE: Angiotensin-converting enzyme.

[a]Diagnoses included: diabetes, chronic obstructive pulmonary disease, myocardial infarction, heart failure, peripheral vascular disease, stroke, chronic renal insufficiency, dementia or Alzheimer disease, connective tissue disease, gastric ulcer, hemiplegia, and hepatic disease.

codes and without any validation process. Additionally, cumulative duration was calculated similarly to the SIDIAP database, this is, regardless of the duration of the prescription. In SIDIAP socioeconomic status and alcohol abuse were further considered, as in BIFAP the former was not available and the information on the latter is scarce. Finally, the main analysis was conducted excluding ever users of amiloride in order to explore the specific contribution of this drug as it is the principal combination with HCTZ.

Secondary analyses were performed in BIFAP for other diuretics with suggested photosensitizing properties such as furosemide, indapamide, and amiloride,[1] but also for other antihypertensives (calcium-channel blockers (CCB), angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEi).[2] These analyses were adjusted for HCTZ use.

All analyses were performed using STATA Release 15.1 (StataCorp, College Station, TX) and R.[35] The study was approved by the scientific committees of BIFAP and SIDIAP, as well as by the Ethics Committee of IDIAPJGOL.

3 | RESULTS

The study cohorts included 5 879 638 subjects in SIDIAP and 6 168 772 in BIFAP. In SIDIAP, we identified 8235 incident cases of MM and 75 096 of KC. The IR by 100 000 persons-years was 15 for MM and 129 for KC. In BIFAP, the number of validated incident skin cancer cases was 4661 for MM and 31 063 for KC (26 000 BCC and 4863 SCC). Further, 5629 patients presented a code for unspecified skin cancer (Figure 1). The IR was 13 for MM and 88 for KC (74 for BCC and 14 for SCC). The proportion of cases confirmed in the validation process was higher for MM (Positive Predictive Value [PPV] 81.6%) than for KC (PPV 73.0%).

Characteristics of cases and controls are presented in Table 1. No major differences were seen between the two databases. Regarding exposure, 30.1% of the population were ever users of HCTZ in SIDIAP and 19.8% in BIFAP, while 5.3% and 1.6% were classified with a high cumulative use (≥50 000 mg), respectively.

3.1 | Risk associated to HCTZ

Figure 2 shows the association between use of HCTZ and the risk of skin cancer. Results on high users of HCTZ with respect to MM were inconsistent between SIDIAP and BIFAP with IRR (95% CI) estimates of 1.25 (1.09–1.43) and 0.85 (0.64–1.13), respectively. However, a dose–response relationship was not observed in any of the two databases (p for trend>0.05). For KC, the risk of ever use was 1.13 (1.11–1.15) in SIDIAP and 1.10 (1.07–1.14) in BIFAP, and the risk for high use was 1.30 (1.26–1.34) and 1.20 (1.12–1.30), respectively. A clear dose–response was observed between cumulative doses of HCTZ and KC risk in both databases. Furthermore, the exposure to HCTZ was associated with an increased risk of BCC and SCC in BIFAP. Compared with never-users of HCTZ, patients with a

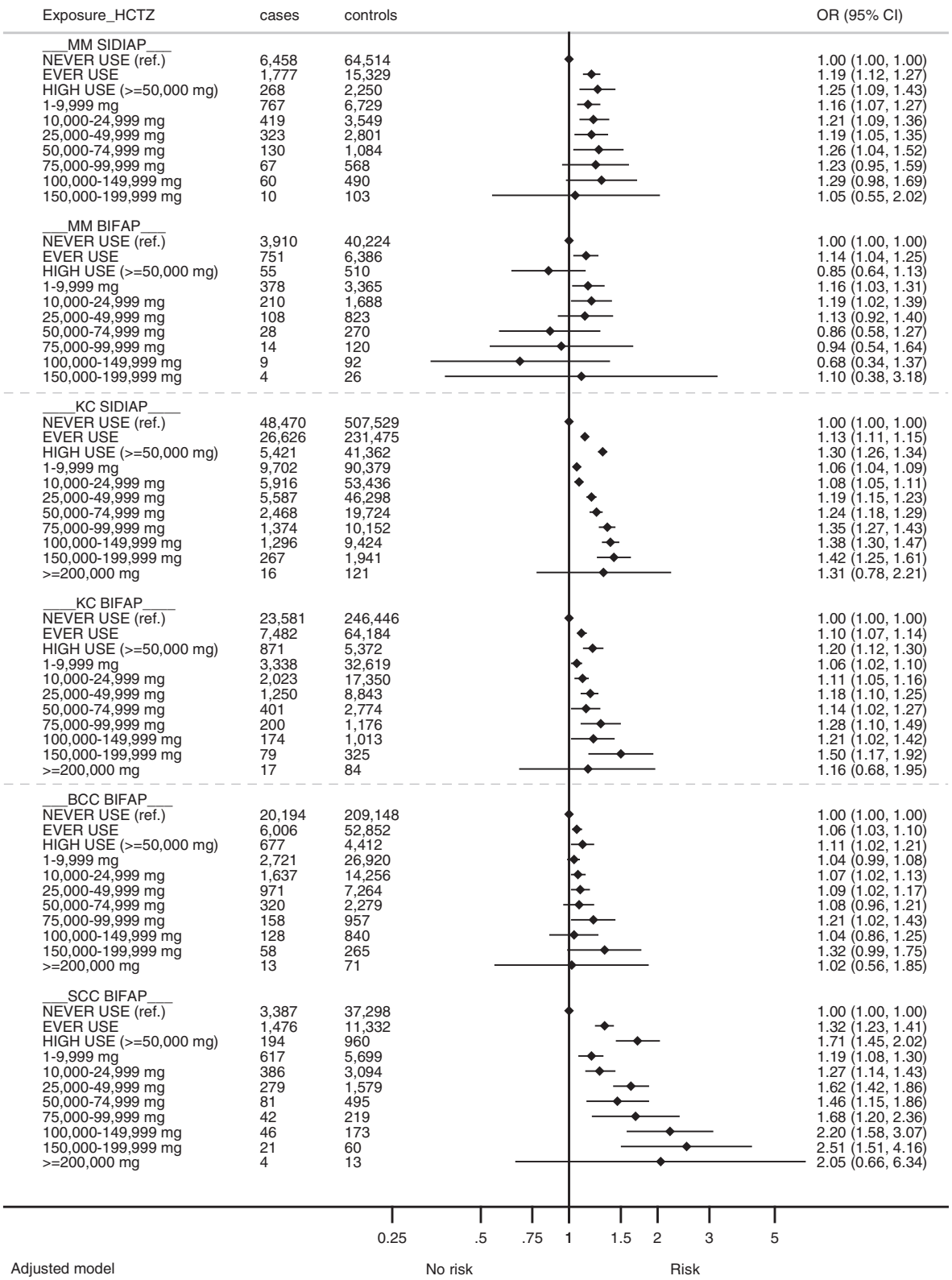

FIGURE 2 Use of HCTZ and risk of skin cancer, by cancer subtype and data source. Abbreviations: MM: Malignant melanoma. KC: Keratinocyte carcinoma. BCC: Basal cell carcinoma. SCC: Squamous cell carcinoma. OR: Odds ratio. CI: Confidence interval. Adjusted for age, gender, time up to index date since first day of register in the database, any use of photosensitizing drugs (topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, methoxypsoralene), any use of drugs with suggested antineoplastic effects (aspirin, non-aspirin non-steroidal anti-inflammatory drugs, statins), any use of glucocorticoids, comorbidity (diagnose of diabetes, chronic obstructive pulmonary disease, chronic kidney disease, myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular accident, dementia or Alzheimer disease, connective tissue disease, gastric ulcer, hemiplegia, liver disease), smoking

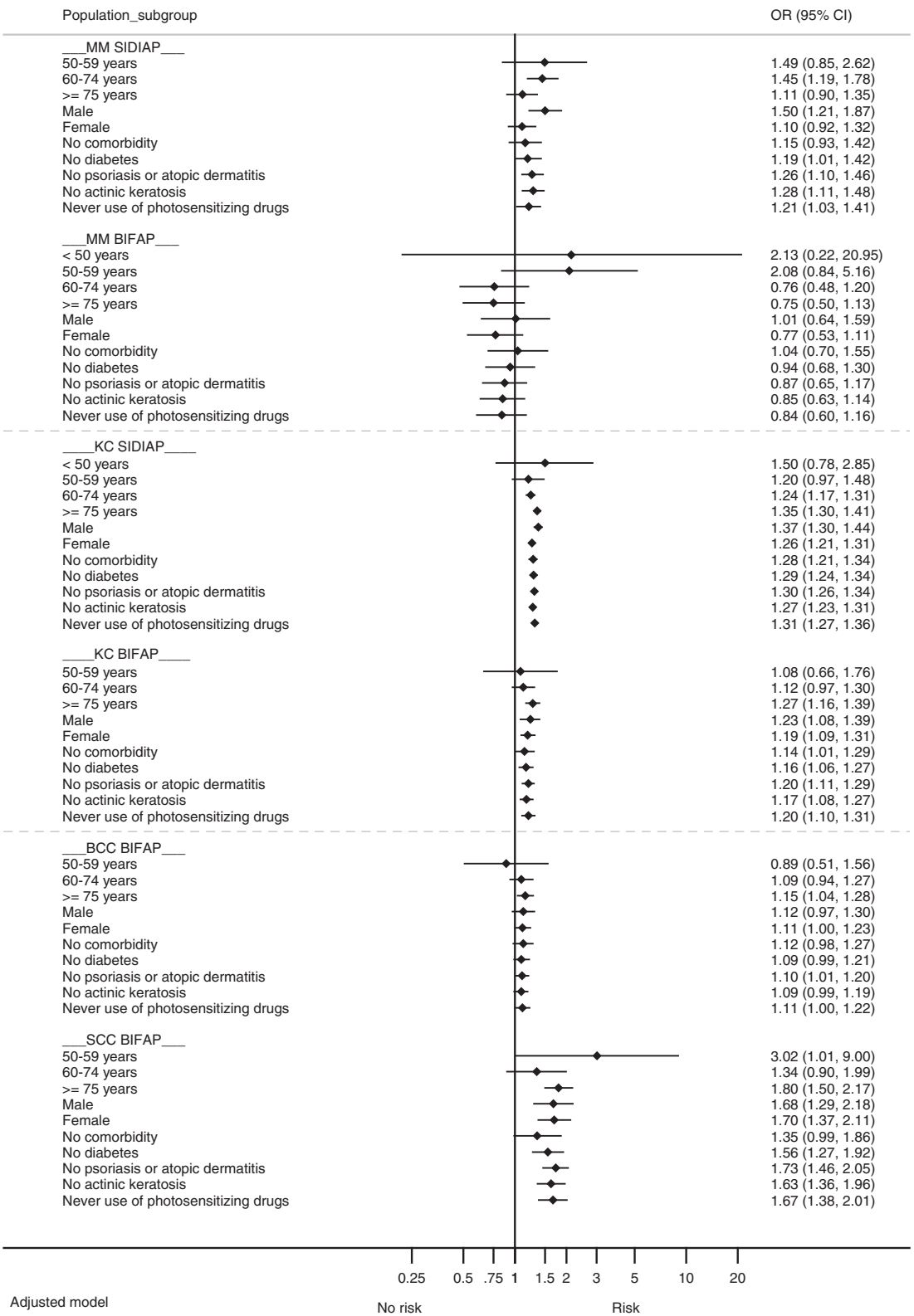

FIGURE 3 High cumulative use (≥50 000 mg) versus never use of HCTZ and risk of skin cancer, by population subgroups. Abbreviations: MM: Malignant melanoma. KC: Keratinocyte carcinoma. BCC: Basal cell carcinoma. SCC: Squamous cell carcinoma. OR: Odds ratio. CI: Confidence interval. Adjusted for age, gender, time up to index date since first day of register in the database, any use of photosensitizing drugs (topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, amiodarone, methoxypsoralene), any use of drugs with suggested antineoplastic effects (aspirin, non-aspirin non-steroidal anti-inflammatory drugs, statins), any use of glucocorticoids, comorbidity (diagnose of diabetes, chronic obstructive pulmonary disease, chronic kidney disease, myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular accident, dementia or Alzheimer disease, connective tissue disease, gastric ulcer, hemiplegia, liver disease), smoking

cumulative dose ≥50 000 mg presented an IRR of 1.11 (1.02–1.21) for BCC and 1.71 (1.45–2.02) for SCC. However, while the relative risk of BCC increased 1% for each 10 000 mg of cumulative dose (p for trend<0.01), the corresponding increase for SCC was 6% (p for trend<0.001). The IRR for unspecified skin cancer was 1.16 (1.09–1.25) for ever use and 1.67 (1.36–2.05) for high use of HCTZ (Table S1 online).

The association between high dose of HCTZ and skin cancer in population subgroups is shown in Figure 3. Only in SIDIAP an increased risk of MM was found, in males, with IRR: 1.50 (1.21–1.87), and in patients 60–75 years old, with IRR: 1.45 (1.19–1.78). On the contrary, an increased risk of KC associated to high exposure of HCTZ was consistently observed in both data sources for subgroups of age and sex, and also among individuals with no history of chronic conditions or skin diseases. Of note, in both databases the highest KC risk was observed in patients older than 75 years, [IRR: 1.35 (1.30–1.41) in SIDIAP and 1.27 (1.16–1.39) in BIFAP], and in men, [IRR: 1.37 (1.30–1.44) and 1.23 (1.08–1.39) respectively]. Lastly, high use of HCTZ was not generally associated to a significant increased BCC risk among population subgroups, but it was associated to increased SCC risk in both men and women and in patients over 75 years old.

In BIFAP, impact measures were calculated using estimated IR and OR for BCC and SCC, showing that high exposure of HCTZ would cause 8 additional cases of BCC and 10 of SCC per 100 000 persons per year. To have one additional BCC or SCC case per year it would be needed to treat 12 323 and 10 288 patients, respectively, long enough to accumulate 50 000 mg of HCTZ (i.e., 6 years approximately, as such amount is equivalent to 2000 DDD). If using published IR for BCC and SCC[36] in Spain instead of the ones obtained in BIFAP, the number of additional cases due to high use of HCTZ would range between 10 and 16 for BCC and 21 to 42 for SCC. Consequently, the number of patients needed to treat with high use of HCTZ to cause one additional case per year would be 6131 to 10 218 in BCC and 2378 to 4815 for SCC.

3.2 | Sensitive and secondary analysis

In BIFAP, using the broader case definition, IRs of MM, KC, BCC and SCC were 16, 120, 99, and 21 respectively, and estimates of risk did not change (Supplementary Table S1). Cumulative HCTZ dose calculation, regardless of the duration of the prescriptions, did not affect estimates of risk notably (Supplementary Table S2). Additional adjustment for socioeconomic status and alcohol abuse did not change results (Supplementary Table S3). When the analysis was restricted to never users of amiloride, the risk of MM and KC associated to high dose of HCTZ remained practically the same: the IRR for MM was 1.20 (1.03–1.40) in SIDIAP and 0.83 (0.52–1.32) in BIFAP, and for KC it was 1.27 (1.23–1.31) in SIDIAP and 1.18 (1.05–1.34) in BIFAP. However, the risk of SCC was notably lower (Supplementary Table S4).

Supplementary Tables S5 and S6 show results of the secondary analysis performed in BIFAP on the associations between other diuretics and antihypertensive drugs and the risk of skin cancer. No relevant association was found between the cumulative high use of any of the studied drugs and the risk of skin cancer.

4 | DISCUSSION

In this study, we found an increased risk of KC associated to HCTZ in two large Spanish databases, with a clear dose response pattern. However, the magnitude of the association differed notably depending on the subtype of KC. For MM, findings were conflicting and with no dose–response observed in any of the two databases.

Results for KC in BIFAP were generally similar to results from a Danish study,[8] in which high use of HCTZ increased the risk of BCC by 1.3 times (1.1 times in BIFAP) and the risk of SCC by four (1.7 times in BIFAP). Recently, studies from the United Kingdom (UK) also using a primary care database,[11–13] showed similar results. In these studies HCTZ was related to KC too, especially to SCC. However, no risk of MM was found. In the Icelandic population[10] HCTZ was also associated with KC and the relative risk was higher for SCC than for BCC. Conversely, in a recent study in a Taiwanese population,[15] HCTZ showed no evidence of increased skin cancer risk, likely due to potential differences in both skin type and behavior between Caucasian and Asian populations.[15] Importantly, in most of the studies, estimates of risk in higher categories of cumulative doses were based on few cases, inferring a certain lack of precision.

Our findings were robust across case definition and methods. IRs in SIDIAP were in line with other publications.[36] In BIFAP, IR was slightly lower for SCC (IR for BCC ranged from 89 to 148 and for SCC from 29 to 59 per 100 000 person-years[36]). This is coincident with the lower PPV found for KC compared to MM. It is likely that cases recorded as unspecified skin cancer mostly corresponded to KC. Of note, risks for unspecified skin cancer were similar to those for SCC. Even assuming a non-differential misclassification of SCC with respect to the exposure, by which risk would be biased towards the null, risk associated to HCTZ was high enough to assume that the association exists. The broader definition of skin cancer applied in sensitivity analyses did not change results.

Our results show that even among never-users of amiloride, high use of HCTZ increased the risk of KC, as already found in the Danish study.[8] However, the specific risk for SCC was not as clear in never-user of amiloride. Of note, in this subpopulation the number of patients exposed to high cumulative use of HCTZ was low, and a possible association between amiloride and SCC[1] could not be ruled out. We did not find an increased risk of skin cancer for furosemide, indapamide or amiloride. However, as amiloride is only available in Spain in combination with HCTZ, adjusting for HCTZ might be over-adjusting and removing some possible SCC risk attributable to the use of amiloride. Out of all antihypertensives studied, while ACEi did not show risk of skin cancer, for CCB and ARB the risk for KC was marginal, with confidence intervals close to the null. To further elucidate the effects of these drugs on skin cancer, we examined *post-hoc* the risk restricted to never-users of HCTZ (Supplementary Table S7),

revealing that the cumulative high dose was not independently associated to any skin cancer subtypes for any of these drugs (the restriction could not be done for amiloride).

One limitation of this study is the lack of direct or indirect measures of UV exposure. Clustering of risk behaviors favoring skin cancer among users of diuretics might be possible, but HCTZ users are not expected to differ substantially from the background population in terms of sun exposure habits, and the likely impact of this factor would be limited. Differences in sun exposure patterns between the study populations are also not expected due to similarities in the location of the regions included and the nature of both databases. Furthermore, consistent results between different databases of different countries with diverse skin UV sensibility strengthen the potential of HCTZ for increasing the risk of KC. A potential limitation in BIFAP is the use of prescription information for drug exposure when drug dispensing was not available (40% were prescriptions). However, antihypertensives are chronically used, so primary nonadherence is supposed to be low, especially for single-pill combination therapies.[37] Lastly, analyses with different lengths of lag time were not conducted.

In conclusion, we find that, in the Spanish population, a high cumulative dose of HCTZ was related to an increased risk of KC, in particular SCC, with a clear dose–response pattern. It confirms results found in previous studies and therefore regulatory measures already considered, which advised on adequate UV protection and a prompt recognition and treatment of suspected lesions.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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