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REVIEW

Hydrochlorothiazide use is associated with the risk of cutaneous and lip squamous cell carcinoma: A systematic review and meta-analysis

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Abstract

Purpose The aim of this study is to investigate the association between hydrochlorothiazide (HCTZ) use and the risk of cutaneous and lip squamous cell carcinoma development.

Methodology We performed a systematic review and meta-analysis of case–control studies. We searched the Cochrane Library, PubMed, Scopus, Web of Science and LILACS. This study was registered in PROSPERO under protocol CRD42019129710. The meta-analysis was performed using the software Stata (version 12.0).

Results A total of 2181 published studies referring to the theme were identified, from which six were included in this systematic review. Men were more frequently affected by cutaneous and lip squamous cell carcinoma than women, with a 1.42:1 ratio. The mean age for cutaneous and lip squamous cell carcinoma development was 73.7 years. This meta-analysis demonstrated a chance of developing cutaneous and lip squamous cell carcinoma in any region of the body in hydrochlorothiazide users of 1.76-fold higher than in non-users. In addition, a risk factor of 1.80 higher (CI 95% = 1.71–1.89) of cutaneous squamous cell carcinoma in the head and neck region was observed in HCTZ users. Moreover, in the analysis of the dose used, the chance of developing squamous cell carcinoma was 3.37-fold lower when the concentration of HCTZ used was less than 50,000 mg.

Conclusions Our results confirm the association between the use of hydrochlorothiazide and the cutaneous and lip squamous cell carcinoma development.

Keywords Diuretics · Hydrochlorothiazide · Photosensitising reaction · Skin cancer · Carcinoma squamous cell · Nonmelanoma skin cancer

Introduction

Cutaneous squamous cell carcinoma (CSCC), and lip squamous cell carcinoma (lip SCC) are originated from epithelial keratinocytes [1]. CSCC accounts for about 20% of non-melanoma skin cancer (NMSC) [2], while lip SCC represents 25–30% of all oral cancers [3]. Most primary CSCC are located on the head and neck [4]. Both CSCC and lip SCC have a strong correlation with UV radiation [5] and affect mainly fair-skinned older men with long-term or chronic exposition to

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sunlight [1, 6]. Cutaneous and lip SCC are caused by genetic and environmental risk factors [7–9].

Another risk factor is the use of photosensitive drugs, once their metabolites are able to absorb UV radiation specially in the skin [10]. One of these medications is hydrochlorothiazide (HCTZ), an antihypertensive agent belonging to the thiazide diuretic class, which is one of the most commonly prescribed drugs for cardiovascular disorder control [11]. HCTZ may cause a variety of photosensitive eruptions, including over-reaction to sunburn and dermatitis as side effects [12]. The photosensitivity effect of HCTZ occurs in the UVA (320–400 nm) and UVB (290–320 nm) ranges, through a mechanism that involves an interaction between a chemical agent and light [10, 13]. This reaction generates free radicals or induces directly damage to the cell's DNA, rendering cells more susceptible to malignancy [13, 14].

In this context, it has been suggested that the chronic use of HCTZ to treat systemic diseases favors the development of malignant skin disorders, including cutaneous and lip SCC. Therefore, the aim of this paper is to investigate the association between the use of HCTZ and the risk of cutaneous and lip SCC through a systematic literature review associated with a meta-analysis.

Methodology

Focused question

The focused question of this systematic review was obtained according to the PECO acronym: Do participants (P) using hydrochlorothiazide (E) have higher risk compared to those not using it (C) of developing squamous cell carcinoma (O)?

Search strategy

This study was designed according to the 2009 "preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement" guidelines [15], previously registered at the International Prospective Register of Systematic Reviews (PROSPERO) under protocol no. CRD42019129710. A systematic review was performed from the PUBMED, SCOPUS, WEB OF SCIENCE, Cochrane Library and LILACS databases using the following search terms in titles and abstracts (also in combination with MESH terms): "Carcinoma, Squamous Cell", "Squamous Cell Carcinoma of Head and Neck", "Neoplasms, Squamous Cell", "Squamous Cell Carcinoma of Head and Neck", "Hydrochlorothiazide", "Antihypertensive Agents", "Sodium Chloride Symporter Inhibitors" and "Diuretics". In addition, topic-related free terms were added, using the boolean operators "AND" and "OR" to combine search terms (Supplementary Table 1). No language or year restrictions were used in the literature search. The research was limited to human studies. Manual searches were performed from the reference list of included articles in order to optimize and broaden the search strategy.

Eligibility criteria

The following inclusion criteria were used for article selection: (i) cohort studies or case–control studies; (ii) patients diagnosed with squamous cell carcinoma; (iii) patients using hydrochlorothiazide; (iv) studies reporting the odds ratio (OR) and/or risk ratio with corresponding 95% confidence intervals (CIs) or sufficient data for this calculation. Therefore, studies using other antihypertensive drugs, in vitro studies, case-study publications, case series, letters to editors, literature reviews, and any other study which did not meet the inclusion criteria were excluded.

Study selection

The whole selection process was performed by two of the authors independently. The first stage of the selection consisted of removing the duplicates and, subsequently, the resulting titles and abstracts were reevaluated in order to discard unrelated reports, according to the established inclusion and exclusion criteria. These steps were performed using the *Mendeley Desktop* software. After this preliminary screening, the remaining full-text studies were downloaded and evaluated concerning eligibility. At this point, a third author participated to solve divergencies between the two reviewers. Finally, irrelevant articles were removed during the final screening stage against the above criteria, and the remaining studies were selected for the qualitative synthesis.

Data extraction

The included studies were reviewed and the following data summarized: (1) name of first author; (2) year of publication; (3) geographic location of the study; (4) study design; (5) medication; (6) dose; (7) drug use period; (8) histological type; (9) age group; (10) sex; (11) sample; (12) inclusion criteria; (13) exclusion criteria; (14) stratification; (15) localization or proportion on head and neck.

Quality evaluation

A systematic assessment of the risk of bias in the included studies was performed following the recommendations described by Fowkes and Fulton [16]. The purpose of these

guidelines is to provide the means to perform a critical analysis of the assessed studies, carefully investigating items such as study design, sample representativeness, validity, reproducibility, sample loss, and other types of bias. For each item, the reviewers assigned scores that represented a major problem (++), minor problem (+), no problem (0), or not applicable (NA).

Data analysis

Data related to the use of HCTZ and its association with SCC and head and neck SCC were evaluated from the studies carried out by Jensen et al. [17], Friedman et al. [18], Pottergard et al. [19], Pedersen et al. [20] and Morales et al. [21]. In addition, an evaluation of the used dosages of HCTZ and the risk of cutaneous and lip SCC was performed assessing the studies carried out by Pottergard et al. [19], Pedersen et al. [20] and Morales et al. [21]. The software *Stata* (version 12.0) was used for the meta-analysis, using the "metafor" command for a random effects model. Heterogeneity was assessed by Chi-square test ($\chi 2$) and its magnitude by I^2. A significance level of 5% was adopted for all tests.

Results

Included studies

Initially, 2181 published studies were identified through a systematic database search, and 2081 full-text articles were selected after duplicate removal. After a thorough review, 2069 articles were excluded for not meeting the inclusion criteria and 13 full-text articles were re-evaluated for eligibility. In the end, six met the eligibility criteria and were included in the systematic review. The study selection process is displayed in Fig. 1.

Characteristics of the included studies

The six surveys were carried out in the last ten years (2008 to 2020) and consisted in case–control studies, as presented in Table 1. The case and control selection followed inclusion and exclusion criteria available in some articles [17–21] (see Table 1). The only study which takes into account ethnic factors for the exclusion of patients was the work of Friedman et al. [18], in which only non-Hispanic white individuals were selected.

The sample was stratified into smokers, former smokers, never smokers and not informed [18, 21] and, in three studies, stratified by family history of diabetes, chronic obstructive pulmonary disease, chronic renal failure or conditions associated with high alcohol consumption, educational level, and Charlson's comorbidity index [19–21]. Body mass index was analyzed in one study [21]. Skin reactions, sun exposure from 9 am to 5 pm, painful burns, the use of tanning lamps and radiation treatment were also evaluated in another study [22].

Regarding HCTZ use, this drug was used as a mono- or combination therapy. The combination drugs were amiloride [17, 19, 20], triamterene (18,22), lisinopril, nifedipine and atenolol [18], other non-diuretic antihypertensives [20, 21]. HCTZ was used in a variable range of doses among the studies. Criteria such as "never-use", "ever-use", ≥ 25 000 mg (19) or "high use" (≥ 50000 mg) [20, 21] were adopted, as well as the number of received HCTZ prescriptions with or without combination therapy [18]. The use of HCTZ established by a linear increase by 10.000 mg was only used in one study [17]. The use period of HCTZ prior to the cancer diagnosis ranged from 2 to 10 years [17–22].

Regarding gender, men were more frequently affected by SCC than women, with a 1.42:1 ratio. The mean age presenting SCC was of 73.7 years old [17–21]. Only Robinson et al. [22] did not report the mean age of the participants, but indicated that most individuals diagnosed with SCC ranged from 61 to 70 years old (44.1%). The proportion of head and neck SCC was 63% [17]; 100% on the lips [18, 19]; 56.5% [22] and 37.73% [20]. Concerning outcomes associated with HCTZ, the study carried out by Jensen et al. [17], from the diagnosed SCC cases 1129, 159 used HCTZ. Friedman et al. [18] studied 712 SCC cases, where 103 patients used HCTZ. Robinson et al. [22] assessed 1599 cases of SCC, but the number of cases related only to the use of HCTZ was not reported. Pottegard et al. [19] evaluated 139 SCC cases related to the use of HCTZ, of which 14.8% presented high use of HCTZ. Pedersen et al. [20], assessed 1812 SCC cases that made use of HCTZ. Finally, Morales et al. [21] evaluated 7560 cases of SCC, 102 of them used HCTZ.

Quality assessments

In this systematic review, the methodological analysis of the articles followed the guidelines proposed by Fowkes and Fulton [16] (Supplementary Table 2). None of the studies reported losses and all results corresponded to the objectives. Regarding the sampling, all studies were classified as without risk of bias, since all authors evaluated participants who developed SCC and either used HCZT or not. No sample calculations were reported in the assessed studies. Nevertheless, all articles reported a representative number of participants.

Considering the inclusion and exclusion criteria used, some authors excluded or adjusted potentially confounding factors of all participants by stratified analysis, especially concomitant use of other photosensitizing agents [19–21], immunodeficiency [17–21], smoking [18, 21], sun exposure

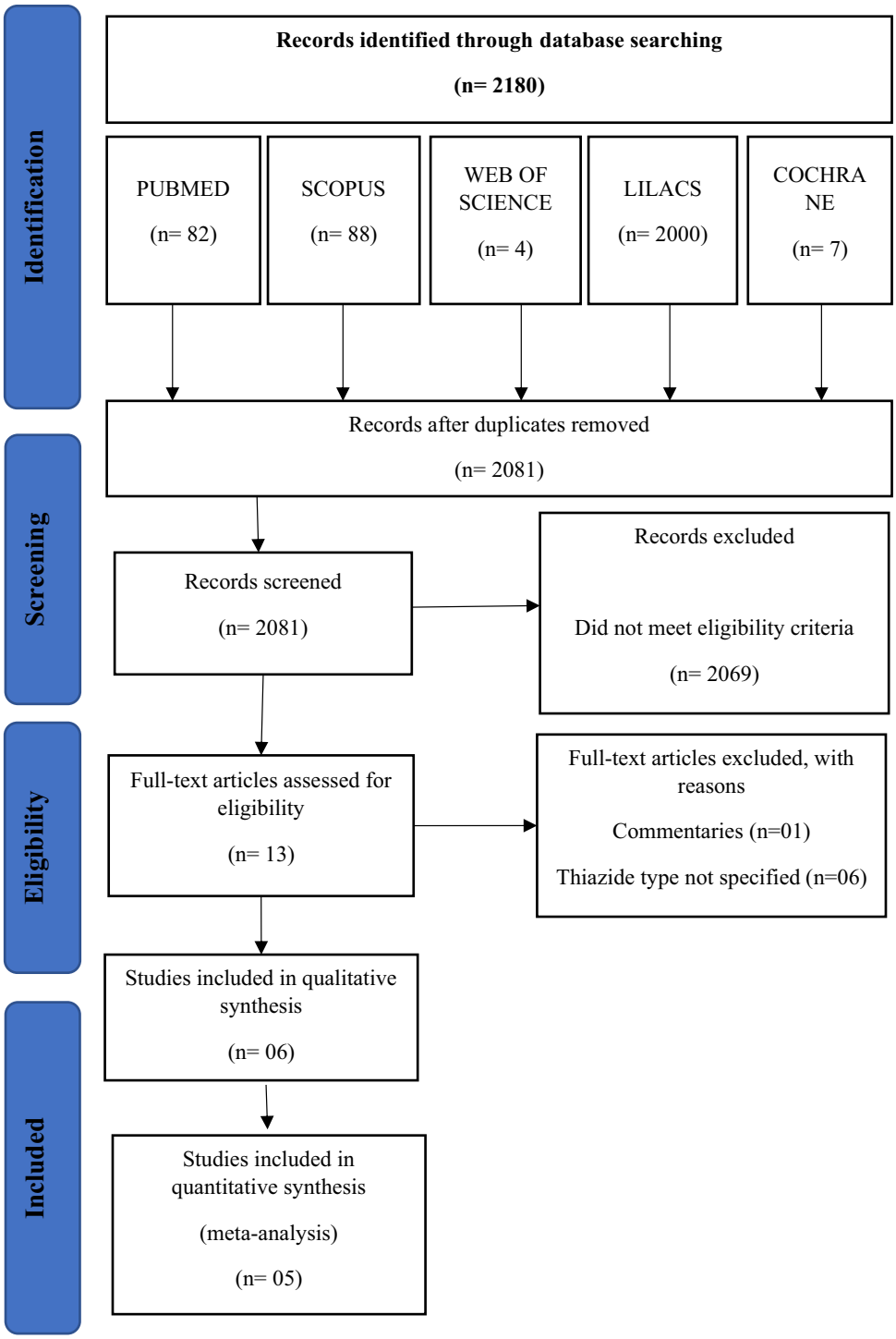

Fig. 1 Flow diagram of literature searches according to the PRISMA statement

time [22], skin phenotype [22] and socioeconomic variables by educational level [19, 20]. Studies that respected six or five of these criteria were considered to be without risk of bias; those who respected four or three criteria were considered to have a moderate risk of bias [19–21], and two or one were classified as high risk of bias [17, 18, 22].

The correspondence between cases and controls were similar and, thus, considered without risk for bias. As for comparable characteristics, all authors appropriately matched age, gender and geographic location [17–22]. However, the authors did not report whether the data were analyzed by more than one evaluator at different times and whether the evaluators were calibrated. None of the authors included death as an analysis variable [17–22]. The main biases found in the studies were selection bias [17, 18, 22], information bias [22], memory bias [22] and instrument bias [22].

Table 1 Summarized data collated from the selected studies

Authors	Geographic location	Study Design	Inclusion diagnostic criteria	Exclusion diagnostic criteria	Exposed/ unexposed total	Outcome (sample) associated with HCTZ	Mean age, y	Sex M/F	Medication (HCTZ or combination)	Dose used	Time used	Stratification	Localization or proportion on head and neck
Jensen et al. [17]	Denmark	case–control	Primary diagnosis of BCC, SCC or MM from 1989 to 2003	Use of photosensitising diuretics < 1 year and chronic medical conditions	Case: 1 129 Control:4 516	SCC (159)	77y	NI	HCTZ and combination (Amiloride and HCTZ)	10 000 mg	Prescriptions > 1 or > 5 year before diagnosis	-	63% SCC
					Case: 5 964 Control:23 856	BCC (542)	69y	NI					54% BCC
					Case: 1 010 Control: 4040	MM (98)	59y	NI					17% MM
Friedman et al. [18]	USA	case–control	Non-Hispanic whites	Solid organ transplant, HIV positive, Non-white race/ ethnicity	Case: 712 Control: 20 904	SCC (103)	68y	530/182	HCTZ and combination (HCTZ and triamterene, lisinopril, nifedipine, and atenolol)	No HCTZ Prescriptions; ≥ 3 HCTZ prescriptions, unadjusted; ≥ 3 HCTZ prescriptions, adjusted	< 1-Year Supply; 1-Year to < 5-Year Supply; ≥ 5-Year Supply	Cigarette smoking	100%
Robinson et al. [22]	USA	case–control	Residents of New Hampshire, speak English, have a listed telephone number, and between the ages of 25 and 74 at the time of diagnosis	NI	Case: 1 599 Control: 1 906	NI (SCC)	61-70y[a]	987/612	HCTZ and combination	NI	non-users, > 1 month and < 7 years, ≥ 7 years overall	Skin reaction, Lifetime warm month hours sun exposure 9am–5 pm, painful sunburns, Tanning lamp use, Radiation treatment	56.5%
					Case: 1 567 Control: 1 906	NI (BCC)	41-50y[a]	794/773					59%

Table 1 (continued)

Authors	Geographic location	Study Design	Inclusion diagnostic criteria	Exclusion diagnostic criteria	Exposed/ unexposed total	Outcome (sample) associated with HCTZ	Mean age, y	Sex M/F	Medication (HCTZ or combination)	Dose used	Time used	Stratification	Localization or proportion on head and neck
Pottegard et al. [19]	Denmark	case–control	Histological diagnosis	No histological diagnosis, Previous cancer, Migration, Organ transplantation, use of azathioprine, or HIV diagnosis	Case: 633 Control: 63 067	SCC (139)	72y	426/207	HCTZ and combination (HCTZ and amiloride)	Never-use, ever-use, high use (≥ 25 000 mg)	No use; 0–1 year; 1–2 years; 2–3 years; 3–5 years; 5 + years	Medical histories of diabetes, chronic obstructive pulmonary disease, chronic renal insufficiency, or conditions associated with heavy alcohol consumption, education, Charlson comorbidity index,	100%

Table 1 (continued)

Authors	Geographic location	Study Design	Inclusion diagnostic criteria	Exclusion diagnostic criteria	Exposed/ unexposed total	Outcome (sample) associated with HCTZ	Mean age, y	Sex M/F	Medication (HCTZ or combination)	Dose used	Time used	Stratification	Localization or proportion on head and neck
Pedersen et al. [20]	Denmark	case–control	Danish residents with histologic verification of their first diagnosis of SCC or BCC of the skin between January 1, 2004, and December 31, 2012	SCC of the lip, previous skin or other cancer diagnoses before the first diagnosis of BCC or SCC, no resided in Denmark for at least 10 consecutive years, record of organ transplantation, HIV diagnosis, or use of azathioprine, cyclosporine, or mycophenolate mofetil	Case: 8 629 Control: 172 462	SCC (1812)	77y	4 803/3 826	HCTZ and combination (HCTZ and amiloride, or non-diuretic antihypertensives)	Never-use, ever-use or high use (≥ 50,000 mg)	At least 2 years	Medical histories of diabetes, chronic obstructive pulmonary disease, chronic renal insufficiency, or conditions associated with heavy alcohol consumption, education, Charlson comorbidity index,	37.73%
					Case: 71 533 Control: 1 430 883	BCC (7900)	66y	33 817/37 716					35.80%

Table 1 (continued)

Authors	Geographic location	Study Design	Inclusion diagnostic criteria	Exclusion diagnostic criteria	Exposed/ unexposed total	Outcome (sample) associated with HCTZ	Mean age, y	Sex M/F	Medication (HCTZ or combination)	Dose used	Time used	Stratification	Localization or proportion on head and neck
Morales et al. [21]	United Kingdom	case–control	Start of the study period (01.01.1999); the practices acceptable mortality reporting date; date of registration with a general practice + one year	No previous cancer diagnosis, no prior record of organ transplantation; HIV diagnosis; or use of immunosuppressan	Case: 7 560 Control: 151 194	SCC (102)	74.8y	4 545/3 015	HCTZ and combination	1–24 999 mg; 25 000–49 999 mg; ≥ 50 000 mg	2 years; 5 years; 10 years	Use of drugs with suggested photosensitizing properties or antineoplastic effects, history of alcohol abuse, diabetes and chronic obstructive pulmonary disease, Charlson comorbidity Index, smoking status, body mass index	NI
					Case: 89 088 Control: 1 781 712	BCC (651)	68.3y	45 581/43 507					
					Case: 11 185 Control: 223 700	MM (61)	58.2y	7 820/3 365					

SCC squamous cell carcinoma, *BCC* basal cell carcinoma, *MM* malignant melanoma, *HCTZ* hydrochlorothiazide, *NI* not informed

[a]Robinson et al. [22] stratified the ages into age groups, so the mean age could not be calculated

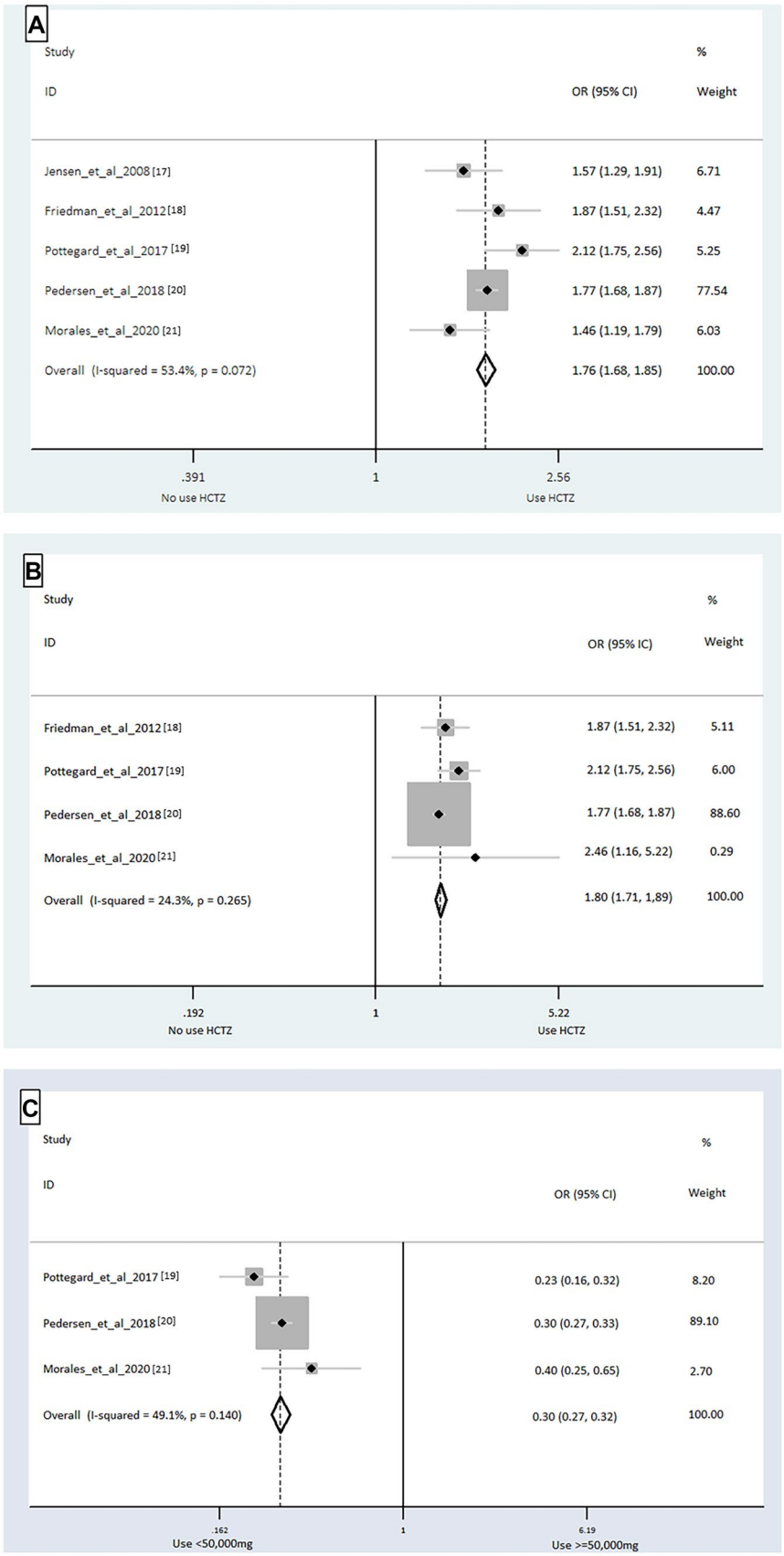

Fig. 2 (**A**) Risk of developing squamous cell carcinoma in any region of the body; (**B**) Risk of squamous cell carcinoma only in the head and neck region among patients who used hydrochlorothiazide, compared to patients who did not use this drug; (**C**) Risk of development of squamous cell carcinoma in any region of the body for patients who used hydrochlorothiazide concentrations < 50,000 mg compared to those who used less than ≥ 50,000 mg of the drug

Meta-analysis

Figure 2 shows the effects of all studies included in the meta-analysis. A risk factor of 1.76 (95% CI = 1.68–1.85) higher for the development of SCC for any location of the body was observed when the patient used HCTZ (Fig. 2A). Individuals who used HCTZ displayed a risk of developing head and neck SCC of 1.80 higher (CI 95% = 1.71–1.89) when compared to individuals who did not use HCTZ (Fig. 2B). Figure 2C indicates that the chance of developing SCC in HCTZ users is 3.37-fold lower when the concentration of HCTZ used is less than 50,000 mg.

Discussion

This systematic review and meta-analysis of published observational studies demonstrates that the use of HCTZ is significantly associated with an increased risk of cutaneous and lip SCC [17–21]. This drug has been classified as a possible carcinogen by the International Cancer Research Agency [23]. As the exposure to UV light increases cell DNA damage, long-term use of HCTZ leads to a higher likelihood of skin malignancy, such as the development of NMSC [24].

Skin neoplasms are most commonly found in the head and neck region, as a consequence of the fact that this region to be particularly exposed to UV radiation [25]. In this meta-analysis, the risk of cutaneous SCC in the head and neck region was higher in HCTZ users than in non-users, showing a low heterogeneity (<50%) [26]. Moreover, the meta-analysis considering drug concentration and the meta-analysis considering CSCC anywhere in the body were performed and indicated an increased risk associated with the use of HCTZ, resulting, respectively, in low and moderate heterogeneity (< 50%; > 50%−≤ 75%) [26]. This degree of heterogeneity validates the combination of information and provides a reliable risk outcome based on the collected data.

The incidence of cutaneous and lip SCC varies widely across geographical areas, as a consequence of the variability in solar irradiance, skin color, sun-exposure habits, cultural and socioeconomic factors [7, 8]. All studies included were conducted in the northern hemisphere: two studies were done in the USA [18, 22], one in England [21] and three in Denmark [17, 19, 20]. Although three studies were carried out in Denmark, they were different in the evaluation period, country region, size and sample used, and location of the lesion, which guarantees the originality of the results. Characterizing the location where the studies are conducted is important because countries closer to the equator are more exposed to solar radiation, such as Brazil and Australia [25], raising the hypothesis that an even greater risk could be found in locations close to this region.

The occurrence of cutaneous and lip SCC among male individuals is higher as compared to female [17–22, 27]. This seems to reflect the reduced frequency of outdoor occupations and the use of photoprotective cosmetics by female [28]. The prevalence of cutaneous and lip SCC has been observed in people over 50 years of age [17–22], being rare in individuals under 40 years of age. The involvement of older people is partly due to an average accumulation rate of 70,000 h of lifelong sun exposure for SCC development [29, 30]. Although skin color is related to cutaneous and lip SCC development [7, 8] and studies included here were performed in countries composed mostly of fair-skinned individuals, the studies carried out by Jensen et al. [17], Pottegard et al. [19], Pedersen et al. [20] and Morales et al. [21] did not provide information on skin phenotype, which could underestimate a risk association between skin sensitivity to the sun and HCTZ use. Epidermal melanin of darker-skinned groups is a known photoprotective factor, which results in greater filtration of UV radiation along with antioxidant and radical scavenging properties [31].

Identifying factors related to the risk of cutaneous and lip SCC is a step toward elucidating the processes underlying HCTZ-induced carcinogenesis. Hard evidence that immunodeficiency leads to an increased risk of cancer incidence has already been demonstrated, caused by decreased immune surveillance and DNA repair mechanisms [32]. Immunodeficiency was the main confounding factor excluded by the authors [17–21]. However, the exclusion criteria adopted by Robinson were not clearly defined in his study. General lack of exclusion of immunosuppressed patients may compromise the analysis of the cutaneous and lip SCC risk associated with HCTZ use. Other potential predictor of risk of cutaneous and lip SCC is smoking [33, 34]. In a meta-analysis carried out by Leonardi-Bee et al. [35], a marked association between smoking and cutaneous SCC was demonstrated, especially in current smoking patients. In this study, Friedman et al. [18] and Morales et al. [21] also confirmed this association. Stratification or exclusion of smoking patients, as adopted by these authors, must be assumed to demonstrate the effect of HCTZ in cutaneous and lip SCC.

This work presents some limitations. First, some studies may not have been indexed in the searched databases, although a broad search strategy was used, which characterizes a publication bias. Second, the discrepancy in sample size among different studies may have contributed to the observed heterogeneity index among them. Third, the lack of information in some eligible studies on common individual risk factors for cutaneous and lip SCC, such as skin color, amount of UV exposure, and smoking status, comprise an important limitation, since they play, respectively, a protection factor and etiological factor. Fourth, a meta-analysis regarding the drug use time was not possible, and the effects of time appear to be as important as those of dose. Fifth, the

meta-analysis could not be performed in one study, due to the grouping of HCTZ within cardiovascular medications [22].

Implications and recommendations

The findings reported herein imply that HCTZ exerts a cocarcinogenic effect along with UV radiation on the development of these lesions, since HCTZ favors the radiation absorption and, consequently, the resulting photodamage.

However, one question that invariably accompanies this study is: how will these findings translate into clinical practice? Our founds do not represent an absolute contraindication to HCTZ. First and foremost, the social role of a relatively cheap and effective medicine must be recognized. The aim herein is to minimize the impact of HCTZ on skin damages by adopting UV protective procedures and by permanently monitoring patients who make regular use of this drug. Ignoring idiosyncrasies, information on the increased absorption of UV radiation and the possibility of skin rashes after using HCTZ should accompany the medical prescription.

Conclusions

In summary, the results confirm HCTZ as a risk factor for cutaneous and lip SCC. Our study also indicates that the HCTZ dose affects this risk, since patients exposed to smaller doses of HCTZ had a smaller chance of developing cutaneous and lip SCC. We highlight the importance of conducting studies on this topic in other regions of the world, especially in ethnically diverse and tropical countries, such as Brazil. Therefore, we consider this study is important to call the attention of the HCTZ users to the necessity of using UV protective procedures, as well as to guide medical committees and public authorities regarding the importance of monitoring those users.

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Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

Statement of prior presentation The work here has not been previously published

Conflict of interest disclosures The authors declare no conflict of interest during the time involving the work, from initial conception and planning to present.

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