Reviewing the effects of thiazide and thiazide-like diuretics as photosensitizing drugs on the risk of skin cancer

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Background: Thiazide diuretics and particularly hydrochlorothiazide were recently linked to an increased risk of skin cancer, which was attributed to the photosensitizing properties of these drugs. Given the widespread use of thiazide diuretics, a potential skin cancer promoting effect would impose an important public health concern.

Objective: To critically appraise in a narrative review, the association between use of thiazide and thiazide-like diuretics and risk of skin cancer.

Methods: We evaluated chemical structures and photosensitizing potential of selected thiazide and thiazide-like diuretics. Moreover, we searched PubMed up to December 2018 for observational studies assessing the association between use of thiazide or thiazide-like diuretics and risk of skin cancer. Study quality was assessed for major methodological biases.

Results: Commonly used thiazide and thiazide-like diuretics carry resonating structural components, such as sulfonamide groups that contribute to their photosensitizing activity. Overall, 13 observational (9 case–control, 4 cohort) studies assessed the association between use of different thiazide or thiazide-like diuretics and risk of several skin cancer types. Of those, nine studies showed positive associations ranging from 3% increased risk for bendroflumethiazide and basal cell carcinoma to 311% increased risk for thiazide diuretics and squamous cell carcinoma. All studies had important design-related methodological limitations including potential confounding by indication, detection bias, and time-window bias.

Conclusion: Commonly used thiazide and thiazide-like diuretics have photosensitizing potential, and some observational studies with important methodological limitations have linked their use to an increased risk of skin cancer. Well designed observational studies are needed to provide more solid evidence on this possible association.

Keywords: hydrochlorothiazide, pharmacoepidemiology, review, skin cancer, thiazide diuretics

Abbreviations: BFZ, bendroflumethiazide; HCTZ, hydrochlorothiazide; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; RCT, randomized controlled trial; ROS, reactive oxygen species

INTRODUCTION

Thiazide and thiazide-like diuretics belong to the five major drug classes recommended for treatment of hypertension in the 2018 European Society of Cardiology and European Society of Hypertension guidelines [1]. Commonly used thiazide diuretics include hydrochlorothiazide (HCTZ), bendroflumethiazide (BFZ), or bendrofluazide, whereas typical thiazide-like diuretics are chlortalidone and indapamide. Several randomized controlled trials (RCTs) have demonstrated the efficacy of these diuretics in preventing all types of cardiovascular morbidities and mortality [2,3]. Thus, even today, more than 60 years since their introduction, thiazide and thiazide-like diuretics are still considered a backbone of blood pressure-lowering treatment [4].

These drugs have expected potential side effects, particularly when used in higher doses, based on their mode of action including electrolyte disturbances, such as hypovolemia, hypokalemia, hypomagnesemia, hyponatremia, hypercalcemia, or hypochloremic alkalosis. Moreover, their use has also been associated with metabolic side effects based on their potential to increase blood glucose, lipid levels, and uric acid levels [1,4]. Very recently, several studies highlighted another potential safety issue associated with the use of thiazide diuretics; an increased risk of several types of skin cancer [5–8]. The rationale for conducting these studies came from the hypothesis that the photosensitizing properties of thiazide diuretics and particularly HCTZ may contribute to an increased risk of skin cancer [9].

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A potential carcinogenic effect associated with the widespread use of HCTZ or other thiazide diuretics represents a major public health concern. Thus, the aims of this narrative review are to introduce the reader to the basic mechanisms of drug-induced photosensitivity, and to critically appraise the available clinical evidence on a potential association between HCTZ and other thiazide or thiazide-like diuretics and the risk of skin cancer.

PHOTOSENSITIZING DRUGS

Definitions and clinical manifestations

Drug-induced photosensitivity reactions constitute cutaneous adverse events because of exposure to a drug (systemically or topically administered) and sunlight, accounting for approximately 8% of cutaneous adverse events overall [10,11]. The most common manifestation is the appearance of skin eruptions with various shapes and sizes within minutes to hours after exposure in sun-exposed areas. Photosensitive reactions are initiated mainly by exposure to ultraviolet A radiation (320–390 nm) and visible light (390–700 nm) rather than ultraviolet B radiation (290–320 nm) [10,12].

Depending on the underlying pathophysiologic mechanism, drug-induced photosensitivity reactions are classified into phototoxic and photoallergic reactions (Fig. 1). However, in many cases, a drug can induce both types of reactions, and a clear distinction may not be always possible [13]. Phototoxic reactions are more frequent, occur more rapidly, and show a closer correlation to the dose of the photosensitizer and the amount of ultraviolet radiation. Photoallergic reactions are immune-mediated, occur less frequently and in response to low doses, and require prior sensitization [14]. Although phototoxic and photoallergic reactions may share a similar clinical and histologic picture, phototoxic reactions resemble an exaggerated sunburn with erythema, edema and burning sensation in sun-exposed areas, whereas photoallergic reactions are more like eczematous eruptions in nature that can extend to unexposed skin areas [14].

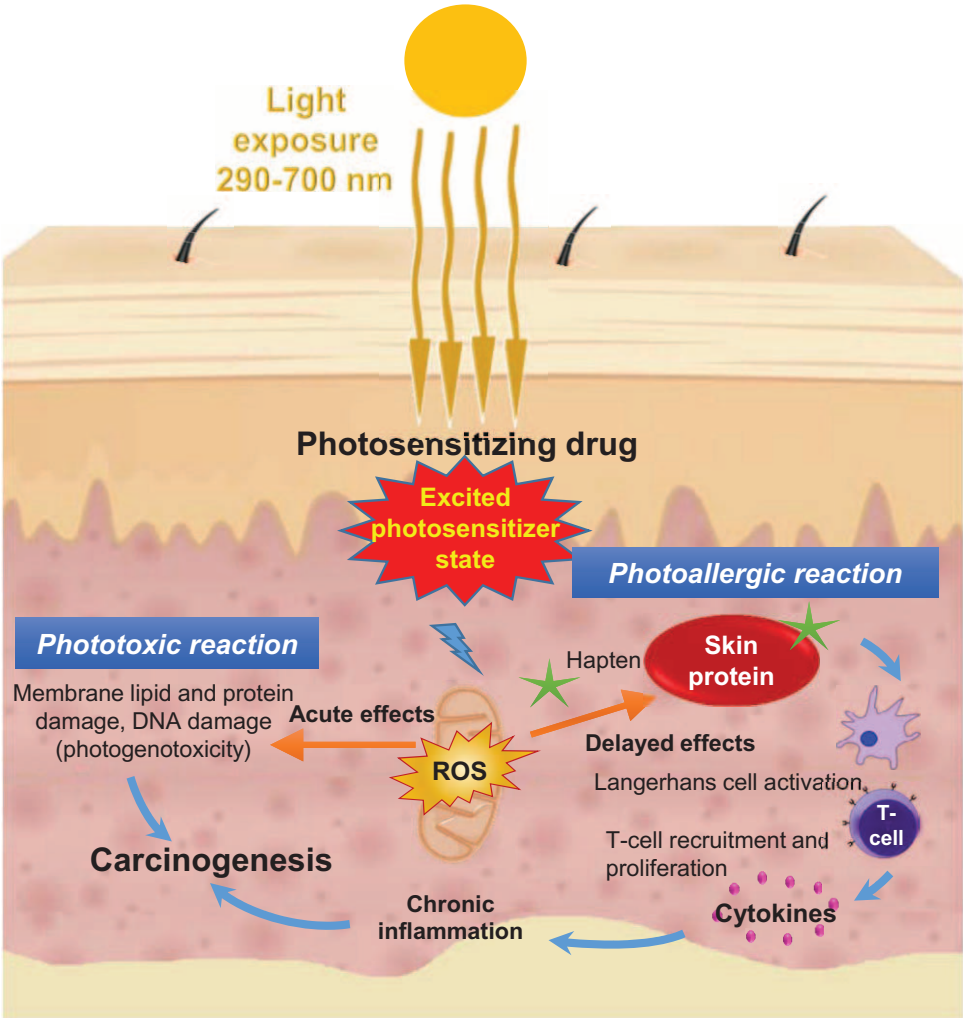

FIGURE 1 Mechanism of drug-induced photosensitizing reactions. A photosensitizing drug in the skin dermal/epidermal layer is photo-excited after absorption of photons of the appropriate wavelength, leading to generation of reactive oxygen species. ROS mediates damage of cellular components, causing acute cytotoxicity effects (=acute phototoxic reaction, left). Alternatively, a photosensitizing drug may act as a hapten that binds to skin proteins in presence of ROS, causing a delayed cell-mediated immunological response (=photoallergic reaction, right). Photosensitizing drugs may thus promote carcinogenesis through DNA damage or by chronic inflammation. ROS, reactive oxygen species.

TABLE 1. Selected antihypertensive agents linked to photosensitive reactions

Class	Specific agents
Diuretics	
Thiazide or thiazide-like diuretics	Bendroflumethiazide, benzthiazide, chlorthalidone, chlorothiazide, hydrochlorothiazide, indapamide, metolazone
Loop diuretics	Furosemide
Potassium-sparing diuretics	Triamterene, spironolactone
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril
Calcium channel blockers	
Dihydropyridines	Nifedipine
Nondihydropyridines	Diltiazem
Beta-blockers	Labetalol, metoprolol, nadolol, timolol
Alpha-blockers	Prazosin
Centrally acting antihypertensive drugs	Clonidine, methyldopa
Direct vasodilators	Hydralazine

Data from [49].

More than 300 types of medications have been implicated in photosensitive (mostly phototoxic) drug reactions including several antihypertensive medications (Table 1) [15,16]. Drug-induced photosensitivity is mainly related to the chemical structure of the compound rather than to the pharmacological effect. Human skin, especially the epidermis, contains several major ultraviolet radiation absorbing endogenous chromophores, such as DNA, urocanic acid and melanins that absorb and deflect ultraviolet light, conferring significant photoprotection to the skin [17]. In general terms, photosensitizers act as chromophores, the chemical structure of which usually constitutes a planar, tricyclic or polycyclic moiety, while having a molecular mass between 200 and 500 Da [14]. Compounds with resonating structures, alternating single and double bonds or with halogenated aromatic rings are likely to cause photosensitive drug reactions [18]. Moreover, a photosensitizer should absorb light within the range of natural sunlight (290–700 nm), generate reactive oxygen species (ROS) upon absorption of ultraviolet radiation, and distribute sufficiently into skin tissue [14].

The sulfonamide moiety presents the common structural link between the antimicrobial sulfonamides, thiazide diuretics, thiazide-like diuretics, but also loop diuretics, such as furosemide. Hence, all diuretics shown in Fig. 2 share the sulfonamide moiety. However, based on the individual structure of each antimicrobial sulfonamide as well as diuretic compound, there are other components that might additionally contribute to their photosensitizing potential (Fig. 2).

Photosensitizing mechanisms

In phototoxic reactions, light exposure to a photosensitizing drug residing in the dermis causes electron excitation,

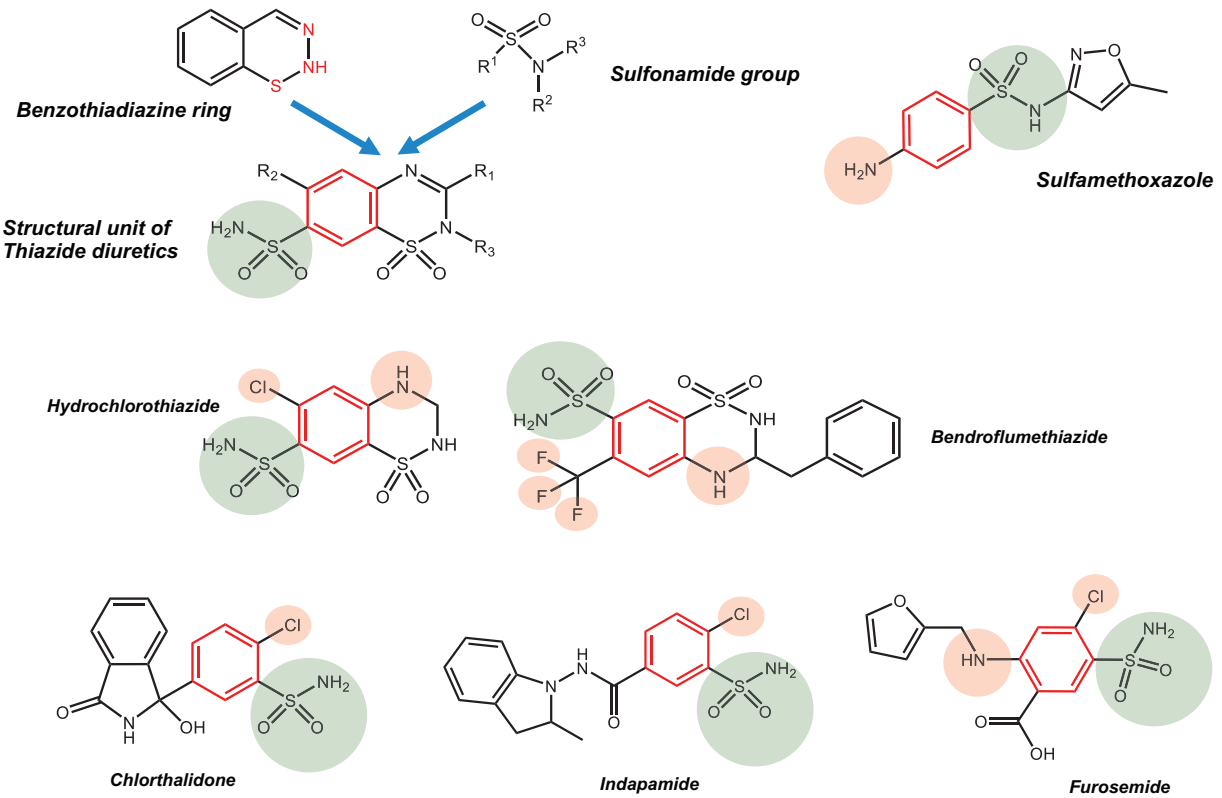

FIGURE 2 Chemical structures of selected diuretics with potential photosensitizing activity. The chemical structures of thiazide diuretics, such as hydrochlorothiazide and bendroflumethiazide are based on a benzothiadiazine ring and a sulfonamide group. The latter is characterized by a sulfonyl group connected to an amine-group (shown in green). The antimicrobial sulfonamide sulfamethoxazole is shown for comparison. The chemical structure of thiazide-like diuretics, such as chlorthalidone and indapamide is also shown. These drugs belong to a diverse group of diuretics that carry also the sulfonamide group but lack the benzothiadiazine ring structure [4]. All diuretics shown including the loop diuretic furosemide have a resonating structure carrying sulfonamide group(s) and additional components contributing to their photosensitizing activity (shown in red), such as halogen atom substituents.

thereby creating unstable singlet or triplet states. Absorbed energy is then released and transferred to molecular oxygen upon returning to a ground state [19]. The discharged energy may cause damage to cellular membrane lipids and proteins via ROS formation, leading thus to inflammation and cytotoxicity. Moreover, this process may also induce DNA damage and thereby exhibit photogenotoxic effects (Fig. 1) [20].

Photoallergic reactions initially parallel phototoxic reactions (Fig. 1), with exposure to light resulting in the modification of the photosensitizer and leading to subsequent ROS formation. The latter facilitates covalent binding of the photosensitizer drug that acts as a hapten to form then a complete antigen [21]. Thus, all photoallergic drugs have phototoxic properties. In the skin, once the antigenic hapten–protein complex is formed, it is processed by Langerhans cells followed by activation and recruitment of T cells ('sensitization phase') [21,22]. Upon subsequent exposure to the perpetrator compound, sometimes with cross-reaction to other related-chemicals, T-cell cytokines initiate an inflammatory reaction that subsequently triggers an allergic response to sunlight ('elicitation phase'). Thus, photoallergy is a delayed-type hypersensitivity reaction [21].

Drug-induced photosensitivity reactions are a function of the inherent photosensitizing activity of the drug, the amount of radiant energy, and drug concentration in the skin [23]. The latter depends on pharmacokinetic characteristics of the specific compound, that also show interindividual variation [24]. Drug concentration in the skin at the time of exposure to light is affected by its plasma concentration, tissue perfusion, drug partitioning into interstitial and cellular compartments, as well as its accumulation and binding to tissues. Thus, drugs with longer plasma half-lives and higher tissue to plasma concentration ratios have a higher potential to induce a photosensitive reaction [25].

Drug-induced photocarcinogenicity

Photosensitizers enhance the vulnerability of the skin to light exposure, the genotoxic and carcinogenic effects of which are well established [23,26,27]. The potential of an exogenous photosensitizing agent to instigate skin tumors occurs either by indirect enhancement of carcinogenic effects induced by light radiation or by mediating a carcinogenic effect upon its own activation following exposure to light ('photochemical carcinogenesis') [23,27,28]. Phototoxicity, photogenotoxicity, and photocarcinogenicity are all mechanistically linked by the activation of photoinstable compounds upon exposure to light (Fig. 1) and subsequent ROS formation, thus inflicting cellular and DNA damage [27]. The latter has been established as the major cause of skin cancer [28]. Although ROS formation is a common underlying pathogenic feature for both phototoxic and photoallergic reactions, the ensuing chronic inflammation may be causally related to cancer development in photoallergic reactions [29]. Therefore, both the resulting oxidative stress and inflammatory responses are important factors contributing to the potential skin cancer risk attributed to photosensitizing drugs.

Preclinical testing for drug-induced photosensitivity

First efforts to establish a regulatory framework to address the safety of drugs regarding their photosensitizing potential, that is, photosafety, were made in the early 1990s [30]. Subsequently, regulatory guidance on the photosafety testing of pharmaceutical products was implemented by the European Medicines Agency and the United States Food and Drug Administration [21]. In 2015, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) completed the guidance document 'S10 Photosafety Evaluation of Pharmaceuticals'. The currently adopted ICH S10 guideline details the timing relative to drug development as well as photosafety assessment strategies of new drug candidates prior to marketing authorization. In this regard, photosafety testing is indicated for compounds that absorb light within an ultraviolet/visible light spectrophotometric range (290–700 nm) if they are locally applied or if they reach the skin or the eyes following systemic exposure [25,31]. However, the majority of antihypertensive drugs that are in clinical use today were developed before systematic photosafety assessments were introduced into regulatory guidelines for drug development. Nevertheless, several antihypertensive drugs including, but not restricted to, thiazide or thiazide-like diuretics are considered as photosensitizing (Table 1).

CLINICAL EVIDENCE

Observational studies on the risk of skin cancer with thiazide or thiazide-like diuretics

For this appraisal, we conducted a single database search (PubMed from inception to 1 December 2018) and identified 13 observational studies assessing the potential association between the use of thiazide or thiazide-like diuretics and the risk of skin cancer (Table 2) [5–8,26,32–39]. Of those, seven assessed the risk of malignant melanoma [7,26,32,33,35,37,38], seven the risk of basal cell carcinoma [5,26,33–35,37,38], seven the risk of squamous cell carcinoma [5,8,26,33,35,37,38], two the risk of lip cancer [36,39], two the risk of Merkel cell carcinoma [6,26], and one the risk of malignant adnexal skin tumors [6]. The studies were from Denmark ($n = 7$) [5–7,26,33,37,39], other European countries ($n = 3$) [32,34,35], or the United States ($n = 3$) [8,36,38]. Most studies applied a case–control design ($n = 9$) [5–7,32,33,35–37,39], while others used a cohort design ($n = 4$) [8,26,34,38].

Six studies assessed the association between the use of HCTZ and the risk of skin cancer [5–7,33,36,39]. Of those, two showed a positive association with malignant melanoma (17% and 32% increased risk) [7,33], two with squamous cell carcinoma (58 and 75% increased risk) [5,33], and two with lip cancer (110 and 119% increased risk) [36,39]. Moreover, one study showed a positive association with basal cell carcinoma (8% increased risk) [5], whereas another did not (either overall or with high cumulative dose) [33]. Finally, one study showed no association with Merkel cell carcinoma or malignant adnexal skin tumors overall but a positive association with high cumulative dose [6].

TABLE 2. Characteristics of observational studies assessing the association between use of thiazide or thiazide-like diuretics and risk of skin cancer

First author	Year	Design	Source population	Exposure	Comparator	Type	OR (95% CI)
Westerdahl [32]	1996	Case–control	General population in South Sweden	Continuous use of any thiazides >1 month	No continuous use of thiazides >1 month	MM	1.4 (0.7–2.8)
Jensen [33]	2008	Case–control	General population in North Jutland County (Denmark)	Any use of HCTZ	No use of HCTZ	MM	1.32 (1.03–1.70)[a]
						BCC	1.05 (0.95–1.16)[a]
						SCC	1.58 (1.29–1.93)[a]
				Any use of BFZ	No use of BFZ	MM	1.08 (0.88–1.32)[a]
						BCC	0.98 (0.90–1.06)[a]
						SCC	1.03 (0.86–1.22)[a]
				Any use of indapamide	No use of indapamide	MM	3.30 (1.34–8.10)[a]
						BCC	0.99 (0.63–1.56)[a]
						SCC	1.20 (0.57–2.54)[a]
Kaae [26]	2010	Cohort	General Danish population	Any use of BFZ	No use of BFZ	MM	1.3 (1.0–1.6)[a]
						BCC	1.0 (1.0–1.1)[a]
						SCC	1.0 (0.8–1.2)[a]
						MCC	0.7 (0.1–5.1)[a]
Ruiter [34]	2010	Cohort	Rotterdam Study in the Netherlands	Any use of thiazides	No use of thiazides	BCC	1.00 (0.95–1.05)[b]
de Vries [35]	2012	Case–control	Hospitals in multiple European countries	Use of thiazides >3 months	Use of thiazides ≤3 months	MM	1.22 (0.77–1.93)
						BCC	1.27 (0.92–1.75)
						SCC	1.66 (1.16–2.37)
Friedman [36]	2012	Case–control	US private health insurance	≥3 prescriptions of HCTZ	<3 prescriptions of HCTZ	LC	2.19 (1.74–2.76)
				≥prescriptions of HCTZ/ triamterene	<3 prescriptions of HCTZ/triamterene	LC	1.98 (1.52–2.58)
Schmidt [37]	2015	Case–control	General Danish population	>2 prescriptions of thiazides	≤2 prescriptions of antihypertensive drugs	MM	1.11 (0.97–1.25)
						BCC	1.05 (1.00–1.11)
						SCC	1.03 (0.91–1.17)
				>2 prescriptions of thiazide-like diuretics[c]	≤2 prescriptions of antihypertensive drugs	MM	1.49 (1.04–2.12)
						BCC	0.98 (0.83–1.15)
						SCC	0.79 (0.51–1.23)
Nardone [38]	2017	Cohort	US academic center	Any use of thiazides	No use of antihypertensive drugs	MM	1.82 (1.01–3.82)
						BCC	2.11 (1.60–2.79)
						SCC	4.11 (2.66–6.35)
Pottegard [39]	2017	Case–control	General Danish population	Ever use of HCTZ	Never use of HCTZ	LC	2.1 (1.7–2.6)
				Ever use of BFZ	Never use of BFZ	LC	1.0 (0.8–1.2)
Pedersen [5]	2018	Case–control	General Danish population	Ever use of HCTZ	Never use of HCTZ	BCC	1.08 (1.05–1.10)
						SCC	1.75 (1.66–1.85)
				Ever use of BFZ	Never use of BFZ	BCC	1.03 (1.01–1.05)
						SCC	1.02 (0.97–1.08)
				Ever use of indapamide	Never use of indapamide	BCC	0.99 (0.92–1.07)
						SCC	0.95 (0.79–1.15)
Pedersen [6]	2018	Case–control	General Danish population	Ever use of HCTZ	Never use of HCTZ	MCC	1.0 (0.6–1.8)
						MAST	1.4 (0.9–2.4)
				Ever use of BFZ	Never use of BFZ	MCC	1.1 (0.7–1.8)
						MAST	0.6 (0.4–1.0)
Pottegard [7]	2018	Case–control	General Danish population	Ever use of HCTZ	Never use of HCTZ	MM	1.17 (1.11–1.23)
Su [8]	2018	Cohort	Hypertensive patients in a US private health insurance	≥2 prescriptions of thiazides	No prescriptions of thiazides	SCC	1.09 (0.99–1.19)[b]
				≥2 prescriptions of thiazide polypills	No prescriptions of thiazide polypills	SCC	1.32 (1.19–1.46)[b]

BCC, basal cell carcinoma; BFZ, bendroflumethiazide; CI, confidence interval; HCTZ, hydrochlorothiazide; MAST, malignant adnexal skin tumors; MCC, Merkel cell carcinoma; MM, malignant melanoma; OR, odds ratio; LC, lip cancer; SCC, squamous cell carcinoma.
[a]Rate ratio.
[b]Hazard ratio.
[c]Including quinethazone, metolazone, and indapamide.

Five studies assessed the association between the use of BFZ and the risk of skin cancer [5,6,26,33,39]. Of those, one study showed a positive association with basal cell carcinoma (3% increased risk) [5], whereas two others did not (either overall or with high cumulative dose) [26,33]. Moreover, two studies showed no association with malignant melanoma (either overall or with high cumulative dose) [26,33], three no association with squamous cell carcinoma (either overall or with high cumulative dose) [5,26,33], one no association with lip cancer (either overall or with high cumulative dose) [39], two no association with Merkel cell carcinoma (either overall or with high cumulative dose) [6,26], and one no association with malignant adnexal skin tumors (either overall or with high cumulative dose) [6].

Six studies assessed the association between the use of thiazide diuretics overall and the risk of skin cancer [8,32,34,35,37,38]. Of those, one showed a positive association with malignant melanoma (82% increased risk) [38], whereas three others did not (no dose–response relation analyses reported) [32,35,37]. Moreover, one study showed a positive association with basal cell carcinoma (111% increased risk) [38], whereas three others did not (one reported no association also with high-cumulative dose) [34,35,37]. In addition, two studies showed a positive association with squamous cell carcinoma (66 and 311% increased risk) [35,38], a third one did not (no dose–response relation analyses reported) [37], whereas in a fourth one, there was an increased risk with thiazide combination pills (32%) but not with thiazide diuretics alone [8].

Finally, three studies assessed the association between the use of indapamide or other thiazide-like diuretics and the risk of skin cancer [5,33,37]. Of those, two showed a positive association with malignant melanoma (49 and 230% increased risk) [33,37], whereas all three showed no association with basal cell carcinoma or squamous cell carcinoma (either overall or with high cumulative dose).

Critical appraisal

Several of the reported studies have important strengths. For example, the source population was often the general population (either nationwide [5–7,26,37,39] or specific geographic regions [32–34]), which can minimize selection bias and augment the generalizability of study findings. Moreover, most studies used cancer registries [5–7,26,32–34,36,37,39] or histologic results [8,35] to ascertain cancer cases, which maximized their sensitivity and specificity. Finally, a few studies (5 out of 13) applied a so-called lag period prior to the date of cancer diagnosis [5–7,36,39]. This approach classifies events as exposed only after a certain period of time following treatment initiation, accounting thus for the 'induction period' between exposure onset and disease onset as well as for the 'latency period' between disease onset and disease diagnosis, both of which are of pivotal importance in the case of cancer [40].

Despite these strengths, the observational studies included in this appraisal have some important methodological limitations (Table 3). First, the comparator group in all studies consisted of unexposed individuals ('nonusers'). Although this approach can maximize power because of the large number of individuals that are eligible for inclusion in the comparator group, it may have introduced confounding by indication and detection bias. Regarding confounding by indication, it is likely that the vast majority of individuals included in the comparator group did not have hypertension. This is problematic, given the possibility that hypertension,

TABLE 3. Major biases of observational studies assessing the association between use of thiazide or thiazide-like diuretics and risk of skin cancer

First author	Year	Design	Information bias	Selection bias	Time-related bias	Confounding
Westerdahl [32]	1996	Case–control	No lag period Detection bias Possible recall bias	Potentially inadequate control selection	Time-window bias	Possible confounding by indication Possible residual confounding
Jensen [33]	2008	Case–control	No lag period[a] Detection bias	No	Time-window bias	Possible confounding by indication Possible residual confounding
Kaae [26]	2010	Cohort	No lag period Detection bias	No	No	Possible confounding by indication Possible residual confounding
Ruiter [34]	2010	Cohort	No lag period Detection bias	No	No	Possible confounding by indication Possible residual confounding
de Vries [35]	2012	Case–control	No lag period Detection bias Possible recall bias	Potentially inadequate control selection	No	Possible confounding by indication Possible residual confounding
Friedman [36]	2012	Case–control	Detection bias	No	Time-window bias	Possible confounding by indication Possible residual confounding
Schmidt [37]	2015	Case–control	No lag period Detection bias	No	Time-window bias	Possible confounding by indication Possible residual confounding
Nardone [38]	2017	Cohort	No lag period[a] Detection bias	No	No	Possible confounding by indication Possible residual confounding
Pottegard [39]	2017	Case–control	Detection bias	No	Time-window bias	Possible confounding by indication Possible residual confounding
Pedersen [5]	2018	Case–control	Detection bias	No	Time-window bias	Possible confounding by indication Possible residual confounding
Pedersen [6]	2018	Case–control	Detection bias	No	Time-window bias	Possible confounding by indication Possible residual confounding
Pottegard [7]	2018	Case–control	Detection bias	No	Time-window bias	Possible confounding by indication Possible residual confounding
Su [8]	2018	Cohort	No lag period Detection bias	Prevalent user bias	No	Possible confounding by indication Possible residual confounding

[a]These two studies used lag periods in sensitivity analyses.

TABLE 4. Selected factors increasing the risk of skin cancer

Patient-related factors	Drug-related factors	Environmental factors
Genetic factors (e.g. family history, specific mutations, such as rs7023329 at 9p21)	Inherent photochemical activity of a photosensitizing drug	Ultraviolet light exposure [i.e. sun-exposure patterns, artificial ultraviolet light exposure (tanning bed)]
White skin	Drug exposure factors: drug pharmacokinetics, individual variations in drug handling, cumulative dose, duration of treatment	History of sun burns
Skin phenotypes (e.g. thickness of stratum corneum)		Use of cosmetics, dyes, personal care products with photoreactive carcinogenic ingredients
Smoking status		Use of protective sun-screens
Immune status		
Co-infection with human papillomavirus		

its severity, or any of its associated risk factors may be associated with the risk of skin cancer. In this setting, it becomes challenging to separate the effect of the drug from the effect of the underlying indication on the observed association. Of note, confounding by indication usually shifts effect estimates away from the null towards increased risks [41].

Regarding detection bias, it is a bias that can lead to spurious associations and is particularly of concern for an outcome, such as skin cancer. Given its asymptomatic nature, any association with thiazide or thiazide-like diuretics could result from increased physician contact, and thus a higher probability of skin cancer detection. Although the studies using a lag period minimized the detection of *early* events, detection bias will persist over time with a comparator group consisting of nonusers from the general population. Of note, one of the studies restricted its population to patients previously diagnosed with hypertension [8]. However, patients in the comparator group were not necessarily treated with antihypertensive drugs ('nonthiazide users'). Thus, confounding by indication and detection bias also apply in the case of this study, albeit probably to a lesser extent. Of note, both biases were cited as potential limitations in a recently published letter to the editor on one of these studies [42].

Finally, a potential limitation of the studies using a case–control design is time-window bias [43]. This time-related bias occurs when cases and controls do not have the same opportunity of exposure. Indeed, time-window bias could have been introduced by not matching on duration of treated hypertension. As such, spurious associations can be observed if the duration of disease is differential between cases and controls. Longer disease duration translates then into a greater opportunity of receiving the exposure of interest, thus biasing the effect estimate [43].

SUMMMARY

Several types of cancer can originate in the skin [44,45], each of which has a multifactorial pathogenesis resulting from the complex interplay between genetic and environmental factors (Table 4). As with most types of cancer linked to environmental exposures, the cumulative exposure to a carcinogen is crucial for cancer development [23] and is modulated by several other factors [35]. Therefore, the potential contribution of photosensitizing drugs, such as thiazide and thiazide-like diuretics needs to be viewed on this background and balanced against their proven beneficial effects in patients with hypertension [1–3].

A recent meta-analysis synthesizing observational studies published until February 2017 that assessed the association between the use of thiazide diuretics and the risk of skin cancer showed a nonsignificant trend towards an increased risk (summary relative risk, 1.31; 95% confidence interval, 0.93–1.83) [46]. However, this analysis lacked a thorough quality assessment of the included studies, as none of the major methodological biases reported here was picked up by the authors. Thus, the validity of this meta-analysis appears to be limited.

The overall inconsistent and puzzling results on the risk of skin cancer induced by thiazide diuretics and especially HCTZ highlight the challenges we face to evaluate and interpret the findings generated by observational studies on drug safety, and the difficulties to draw conclusions for clinical practice. However, RCTs, the gold standard for the assessment of drug efficacy, are not suitable to assess cancer outcomes as safety endpoints. First, given that cancers are rare events developing over many years, RCTs would be unfeasible from a technical point because of the large sample sizes and prolonged follow-up required. Second, such RCTs would also be unfeasible from an ethical standpoint. Thus, the potential cancerogenic risk of drugs can often only be assessed in observational studies.

Observational studies should mainly face the challenge of dealing with confounding because of the absence of randomization. Indeed, the studies included in our appraisal generally went at great lengths in this regard by matching on or adjusting for several potential confounders, such as age, sex, comorbidities, or comedications. However, these studies still had important methodological biases that render the interpretation of their findings difficult. Of note, these biases, mainly confounding by indication and detection bias, are preventable at the stage of study design. For example, using an active comparator, for example, patients treated with antihypertensive drugs without photosensitizing potential, controlling for time-related design aspects, and using methods to minimize detection bias would provide more solid evidence on the possible association between the use of thiazide or thiazide-like diuretics and the risk of skin cancer.

CONCLUSION

All studies evaluated in this narrative review had important methodological biases that render the interpretation of their findings difficult. Intriguingly, available pharmacological evidence shows that photosensitivity is not a unique feature of thiazide diuretics, such as HCTZ but should also be expected among thiazide-like or other diuretics and antihypertensive drugs. Thus, well conducted observational studies are needed to provide more solid evidence on the possible association between the use of thiazide or thiazide-like diuretics as well as other antihypertensive drugs and the risk of skin cancer. Until this occurs, switching from HCTZ to other diuretics, such as chlortalidone is not supported by either pharmacological or epidemiological data. Meanwhile, this controversial discussion should not distract from proven benefits of blood pressure-lowering pharmacotherapy on morbidity and mortality by using the recommended five major drug classes including thiazide and thiazide-like diuretics [1]. In addition, we would like to emphasize that appropriate surveillance and the use of protective measures in patients at risk for skin cancer is per se an important public health issue [47]. This applies, in particular, to populations with high incidence rates of skin cancer [48] and increased exposure to ultraviolet/visible light radiation, including patients treated with potentially harmful photosensitizing drugs.

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Conflicts of interest

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