



Do Thiazide Diuretics Increase the Risk of Skin Cancer? A Critical Review of the Scientific Evidence and Updated Meta-Analysis

Benedetta Bendinelli¹ · Giovanna Masala¹ · Giuseppe Garamella² · Domenico Palli¹ · Saverio Caini¹

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Abstract

Purpose of Review We reviewed the hypothesised mechanisms of skin cancerogenesis for thiazide diuretics; conducted an updated meta-analysis of studies focusing on their association with skin cancer risk; critically appraised the quality of available studies and identified knowledge gaps; and discussed implications for health professionals and patients.

Recent Findings Thiazide diuretics possess well-described photosensitizing properties and a causal association with skin cancer is biologically plausible. The epidemiological evidence is stronger for squamous cell cancer; however, diversity in design among studies, methodological concerns potentially affecting the validity of results, and scarcity of data on dose-relation relationship suggest caution in drawing conclusions. Only few, unbalanced, and/or heterogeneous data exist to date for melanoma and basal cell cancer.

Summary Patients effectively treated with thiazide diuretics are currently not advised to stop treatment, but encouraged to limit exposure to sunlight and regularly check their skin. While endorsing these recommendations, we believe that well-designed studies are urgently needed to overcome persistent knowledge gaps.

Keywords Thiazide diuretics · Cutaneous melanoma · Basal cell cancer · Squamous cell cancer · Risk · Review

Introduction

Skin cancer is one of the most common malignancies in the world. The largest proportion of skin cancer is attributable to

cutaneous melanoma (CM), which arises from melanocytes, and to keratinocyte skin cancer (KSC), whose two main subtypes are the basal (BCC) and squamous cell cancer (SCC). Far less common skin malignancies include Merkel cell carcinoma, cutaneous T cell lymphoma, Kaposi's sarcoma, and others.

Over 350,000 CM cases were estimated to have occurred globally in 2015, with an age-standardized incidence rate of 5 cases per 100,000 persons [1]. Incidence rates of CM rose steeply in the second half of the twentieth century in many countries (particularly among populations of European ancestry) [2]. Highest rates are reported in Australia and New Zealand (40.3 per 100,000 and 30.5 per 100,000, respectively), followed by North America and Northern and Western Europe, while lowest rates are documented in Southern Asia and Africa [3]. CM is the most lethal form of skin cancer (5-year survival rate is below 70% and 30% for stage III and, respectively, stage IV CM) and caused an estimated 60,000 deaths globally in 2015 (approximately 0.7% of all cancer deaths) [4–6]. KSC are the most frequently diagnosed malignancies in humans, with around 1.5 million estimated cases globally in 2016, of which the majority were represented by the BCC subtype [7, 8]. KSC are rarely lethal but, because of

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✉ Saverio Caini
s.caini@ispro.toscana.it

Benedetta Bendinelli
b.bendinelli@ispro.toscana.it

Giovanna Masala
g.masala@ispro.toscana.it

Giuseppe Garamella
giuseppe.garamella@unifi.it

Domenico Palli
d.palli@ispro.toscana.it

¹ Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Via Cosimo il Vecchio 2, 50141 Florence, Italy

² School of Specialization in Hygiene and Preventive Medicine, University of Florence, Florence, Italy

their high incidence, their burden of disease and economic costs (for diagnosis, treatment, and surveillance) are considerable [8].

Non-modifiable risk factors for skin cancer (both CM and KSC) include older age, male gender, family history, and phenotypic characteristics such as fair skin, light eye and hair colour, presence and number of common and atypical naevi, freckling tendency, and type I and II skin phototype [9, 10]. Among environmental factors, exposure to ultraviolet radiation (UV) of natural (occupationally or in leisure time) or artificial sources (sunbeds) plays the most important role in the genesis of skin cancer [11, 12]. Recently, increasing attention has been paid to chemicals that may act as photosensitizing agents, thus having the potential to magnify the carcinogenic effects of the exposure to the UV radiation. Of note, many commonly used medications are known to be photosensitizers: while some of photosensitizing drugs are typically taken for short periods, others may be used for long periods or even lifelong for the treatment of chronic diseases [13]. The latter category also includes anti-hypertensive drugs, whose association with skin cancer risk we recently examined in a literature review and meta-analysis [14•]. Our review covered papers published up to February 2017; after that date, further evidence has appeared in support of an association between the use of thiazide diuretics and skin cancer risk. As a result, national competent authorities and regulatory agencies were urged to conduct safety reviews and take position on the issue. While most drug regulatory agencies cautiously recommended strengthening package inserts on the possible increase in SCC risk associated with the prolonged use of hydrochlorothiazide-containing products, uncertainties remain due to some limitations noted in those studies [15•]. In order to clarify this issue, we conducted an updated meta-analysis of the scientific evidence on the association between thiazide diuretics and skin cancer risk; critically appraised the quality of available studies; reviewed proposed mechanisms of skin carcinogenesis for these drugs; identified knowledge gaps and suggested areas of future research; and discussed implications for health professionals and patients.

Mechanisms of Skin Carcinogenesis of Thiazide Diuretics and Implications of Polypharmacy on Skin Cancer Risk

The capacity to absorb UV and/or visible radiation and, therefore, the potential to cause photosensitization is common to many chemicals, including several drugs. There is some degree of predictability about what drugs possess photosensitizing properties. By and large, two attributes that render a molecule more likely to be associated with skin photosensitivity, namely, a low molecular weight and the presence of aromatic halogen atoms, typically characterize thiazide

diuretics (e.g., hydrochlorothiazide and bendroflumethiazide) [16•]. Most photoactive drugs absorb light in the UVA region (wavelength 315–400 nm), sometimes extending into the visible part of the spectrum (> 400 nm), but a minority of drugs exert their photosensitizing properties also when exposed to radiation in the UVB range (280–315 nm). This minority includes thiazide diuretics as well as other commonly prescribed and over-the-counter medications [16•].

It has been known for a long time the existence of multiple biological mechanisms underlying drug-induced skin photosensitization [17]. For most photosensitizing drugs, skin damage is limited to acute phototoxic reactions, which typically occur within a short time after the first use, and usually cease promptly (i.e., within days) upon stopping the drug. Instead, for some drugs including thiazide diuretics, idiosyncrasy is a possible occurrence, whereby a minority of subjects shows high susceptibility to even low doses of drug (and/or with very low exposure to the UV radiation). Idiosyncrasy is presumably related to genetic predisposition, which can be due to polymorphisms in genes regulating drug metabolism, conjugation and excretion, or antioxidant defence [16•]. In terms of mechanisms of carcinogenesis, thiazide diuretics are thought to act as a chromophore when activated by UV radiation of specific wavelengths, causing direct DNA damage (e.g., pyrimidine dimerization) and possibly inducing a chronic inflammatory reaction of the skin [16•, 18•].

In addition to thiazide diuretics, many other drugs have the ability to induce photosensitivity. Among these, some may be used concomitantly with thiazide diuretics, either to optimize blood pressure control in hypertensive patients (e.g., angiotensin receptor blockers [ARB] and calcium channel blockers [CCB]), or to treat other chronic medical conditions whose prevalence in the population increases in parallel with that of hypertension (e.g., sulfonylureas for the treatment of type 2 diabetes; cardiovascular drugs such as the anti-arrhythmics diltiazem, amiodarone, and sotalol; cholesterol-lowering drugs such as statins; some non-steroidal anti-inflammatory drugs [NSAID]; and others) [14•, 19, 20]. Critically, some of these diseases and/or the drugs used for their treatment have been reported to increase the risk of melanoma and/or KSC, although with varying strength of evidence [14•, 21, 22]. Because of this, we believe that a prior conceptualization (for instance through directed acyclic graphs [DAG]) of the causal chains linking hypertension, concomitant chronic diseases (which can cause hypertension, e.g., diabetes, or be caused by it, e.g., heart failure), use of thiazide diuretics and other photosensitizing drugs, and other factors associated with the risk of those chronic conditions as well as skin cancer (e.g., age and gender) is a prerequisite in order to conduct studies that are as much as possible free from bias and confounding. Based on the above considerations, later in this paper we will conduct a critical appraisal of the studies included in the review and meta-analysis, in order to highlight their strengths

and any potential limitations and help evaluate the quality of the scientific evidence available to date.

Skin Cancer Risk Among Thiazide Diuretics Users: Updated Literature Review and Meta-Analysis

Background and Methods

In our recent literature review and meta-analysis of studies focusing on the association between the use of anti-hypertensive drugs and skin cancer risk, we found a nearly significant 30% increase in skin cancer risk associated with thiazide diuretics use based on findings from six independent studies, with no significant differences between melanoma and KSC, and large between-studies heterogeneity [14•]. Because of the limited number of skin cancer type-specific relative risk (RR) estimates available for the analysis and the large heterogeneity, we refrained from calculating separate summary relative risk (SRR) for BCC and SCC, although the visual inspection suggested that the association with increased risk might be stronger for the latter.

Our previous meta-analysis included studies that were published until February 28, 2017. After that date, other papers reporting on the association between thiazide diuretics and skin cancer risk were published. Therefore, we updated our meta-analysis by extending the literature search to papers published until April 8, 2019. Methods for literature search (databases and search strings) and selection of studies (inclusion and exclusion criteria) were the same as in our previous meta-analysis, to which the reader can refer for consultancy [14•]. In particular, we maintained our rule of not including studies that focused on skin malignancies other than melanoma and KSC (e.g., Merkel cell carcinoma and malignant adnexal skin tumours) [23]. Instead, unlike our previous meta-analysis, we opted to include two papers that were based on SCC occurring on the lips, despite these represent only a minority of all SCC diagnosed in any population.

In terms of statistical methods, measures of relative risk (RR) for the association between thiazide diuretics use and risk of each skin malignancy type were transformed into $\log(\text{RR})$ and pooled to obtain summary relative risk (SRR) and 95% confidence intervals (CI) using random effect models with maximum likelihood estimation (command “metan” in Stata version 14 software, Stata Corp, College Station, USA) [24, 25]. The heterogeneity of RR estimates between studies was quantified using the I^2 statistics, which measures the proportion of variation that is attributable to actual heterogeneity rather than chance [26]. Because of the limited number of eligible studies (see below), we were unable to conduct meta-regression and subgroup analysis when I^2 was above 50% (which is usually assumed to

denote unacceptably large heterogeneity). In those cases, we visually inspected the forest plot and conducted a leave-one-out sensitivity analysis to test the dependency of summary estimates on the inclusion of each study. Finally, we used the Egger and Begg test to assess publication bias [27].

Results: Ever Vs. Never Users, and Dose-Response Relationship

A total of nine papers and one conference abstract were included in the updated meta-analysis [28–37]. Of note, the papers by Kaae et al. and Schmidt et al. were removed from the meta-analysis and replaced with the more recent publications by Pottegård et al. and Pedersen et al., which reported from registry-based studies conducted in the same country (Denmark) during overlapping periods and were based on a much larger number of skin malignancies [22, 36–38].

The SRR for the association between thiazide diuretics use (ever vs. never) and CM risk was 1.17 (95% CI 1.12–1.24), based on four independent RR estimates (Fig. 1). The heterogeneity was low ($I^2 < 0.1\%$), but the results were heavily influenced by the Danish study by Pottegård et al., which was based on 19,723 melanoma cases compared to an overall 1646 cases contributed by the other three studies [28, 30, 33, 36]. Pottegård et al. also reported results stratified according to the histological subtype: the stronger association emerged for nodular (OR 2.05, 95% CI 1.54–2.72) and lentigo malignant melanoma (OR 1.61, 95% CI 1.03–2.50), while a weaker, non-significant association was observed for the superficial spreading subtype (OR 1.11, 95% CI 0.97–1.27) [36].

Study-specific RR estimates for the association between thiazide diuretics use and BCC risk ranged between no effect and a two-fold increase in risk (Fig. 1): this produced a significant association in the meta-analysis model (SRR 1.17, 95% CI 1.03–1.33). However, the between-studies heterogeneity was very large ($I^2 = 90.5\%$) and never fell below 75% in the leave-one-out sensitivity procedure. Finally, we found a nearly two-fold increase in SCC risk among ever vs. never users of thiazide diuretics use (SRR 1.93, 95% CI 1.59–2.35) (Fig. 1), based on seven independent RR estimates from six studies and one conference abstract [30–35, 37]. The leave-one-out sensitivity analysis revealed that most of the large between-studies heterogeneity was accounted for by the Nardone et al.’s study: after its exclusion, the I^2 statistics fell below the threshold of acceptability (from 68.3% to $< 0.1\%$) and the strength of the association was only slightly attenuated while retaining statistical significance (SRR 1.76, 95% CI 1.67–1.85). The further exclusion of the two studies focusing on lip SCC only left the results unchanged [31, 34].

Only five studies among those included in the meta-analysis conducted a dose-response analysis: the main results are summarized in Table 1. Categories of exposure were defined in

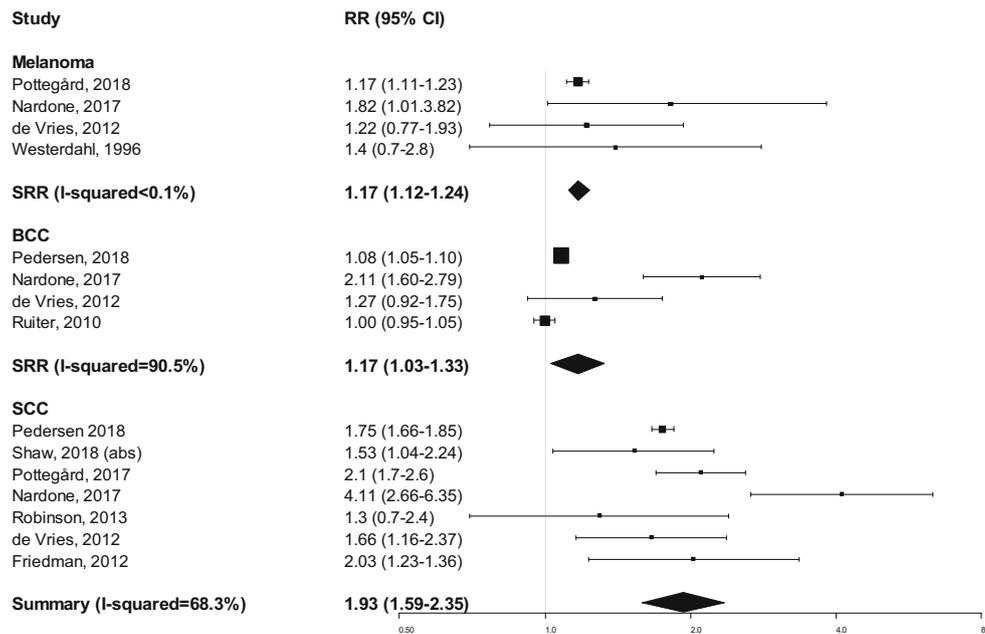


Fig. 1 Association between thiazide diuretics use (ever vs. never) and risk of melanoma, basal cell cancer (BCC), and squamous cell cancer (SCC) of the skin. Study-specific relative risk (RR) and 95%

confidence intervals (CI), and summary relative risk (SRR) obtained through random effects meta-analysis models. See text for details

terms of duration of use (years), cumulative dose (mg), or intensity of use (mg/day) in the different studies. With the sole exception of the study by Ruiter et al., who could not find any evidence that BCC risk correlated with duration of thiazide diuretics use, individuals in the highest category of exposure were generally at increased skin cancer risk compared to non-users [29]. Here as well, the strongest evidence was in support of the association between thiazide diuretics and SCC, although

two of the three studies that performed a dose-response analysis only included SCC of the lip [31, 34].

Type of Thiazide Diuretics

In terms of what thiazide diuretics the study subjects were “exposed” to, four of the studies included in the present meta-analysis considered thiazide diuretics as drug class,

Table 1 Summary of results from studies reporting on the dose-response association between thiazide diuretics users and skin cancer risk

First author, year	Country	No. cases	Definition of exposure	Highest vs. lowest category	RR	95% CI
Melanoma						
Pottegård, 2018	Denmark	19,723	Cumulative dose (mg)	≥ 100,000 mg vs. no use	1.21	1.04–1.42
Basal cell cancer						
Pedersen, 2018	Denmark	6,817	Cumulative dose (mg)	≥ 200,000 mg vs. no use	1.54	1.38–1.71
Ruiter, 2010	Netherlands	522	Duration of use (years)	> 4.5 years vs. no use	1.10	0.77–1.58
Squamous cell cancer						
Pedersen, 2018	Denmark	63,653	Cumulative dose (mg)	≥ 200,000 mg vs. no use	7.38	6.32–8.60
Pottegård, 2017 ^a	Denmark	633	Cumulative dose (mg)	≥ 50,000 mg vs. no use	5.5	4.2–7.2
			Duration of use (years)	> 5 years vs. no use	4.5	3.5–5.9
			Intensity of use (mg/day) ^b	≥ 32.35 vs. 6.25 mg/day	4.9	3.0–7.8
Friedman, 2012 ^a	USA	712	Duration of use (years)	≥ 5 years vs. no use	4.22	2.82–6.31

^a Squamous cell cancer of the lip

^b Analysis restricted to high thiazide diuretics users, defined as patients with a cumulative dose ≥ 25,000 mg

RR relative risk, CI confidence intervals

while one and two studies focused on a single drug, namely, bendroflumethiazide in de Vries et al. and, respectively, hydrochlorothiazide in Friedman et al. and Shaw et al. Instead, in the three registry-based studies conducted in Denmark, a distinction was made between individuals using hydrochlorothiazide and bendroflumethiazide, and risk estimates were provided separately for those two drugs [34–36]. Despite bendroflumethiazide was used by a larger proportion of study subjects in those studies, we opted to include in the meta-analysis the RR estimates obtained among hydrochlorothiazide users, because the latter drug was suspected a priori to convey a stronger skin cancer risk (if any) since it is used at much higher doses and has a longer half-life compared to the former [34]. Indeed, unlike hydrochlorothiazide, there was consistently no significant association between bendroflumethiazide use and skin cancer risk (melanoma, BCC, lip and non-lip SCC) in those three studies, even when maximizing the contrast in the dose-response analysis by comparing subjects in the highest vs. lowest category of exposure. While this appears to confirm the hypothesis that hydrochlorothiazide is the single thiazide diuretics most at risk for skin cancer development, de Vries et al. found instead an increase in skin cancer risk (by 20–30% for melanoma and BCC, and by 60–70% for SCC) among bendroflumethiazide users, which did not substantially diverge from the summary estimates deriving from the meta-analysis [30].

Critical Appraisal of the Quality of the Studies and Implications for the Validity of Results

Ideally, the most robust evidence to answer the question in the title, that is, whether the use of thiazide diuretics increase skin cancer risk, would be provided by a randomized controlled trial (RCT) comparing melanoma and KSC risk between hypertensive patients treated with thiazide diuretics vs. placebo. Such a study cannot be conducted for obvious ethical reasons, and in fact, the totality of the studies included in our review and meta-analysis was observational in nature (Table 2). Those studies differed between one another in many ways, including the specific study design (e.g., cohort or case-control, population- or hospital-based, etc.), the definition and methods of assessment of the exposure, and, most importantly, the covariates that were used to adjust risk estimates (Table 2). We drew a simplified DAG (Fig. 2) to simultaneously illustrate the potential causal chains leading to skin cancer development among thiazide diuretics users, in order to help identify a minimum set of covariates necessary to control for in order to avoid residual confounding and ensure the validity of findings. The DAG includes the exposure (thiazide

diuretics) and outcome (skin cancer) of interest, along with other relevant factors such as demographics, common comorbidities, use of other drugs, and established skin cancer risk factors (i.e., phenotype characteristics and sun exposure). The DAG in Fig. 2 is simplified in that it does not include other potentially relevant factors (e.g., anthropometry, vitamin D, family history, socioeconomic status) that would greatly complicate the picture. In addition, the DAG depicted in Fig. 2 does not distinguish between melanoma and KSC (and its subtypes), malignancies occurring on sun-exposed or sun-shielded skin, etc. Even with this simplified DAG, it is relatively straightforward to infer that controlling for demographics (age, gender, ethnicity, etc.), phenotypic characteristics and history of sun exposure may not be sufficient to avoid residual confounding, because other pathways remain open via the presence of comorbidities (e.g., cardiovascular diseases and diabetes) and the drugs used to treat them, and through the use of other anti-hypertensive drugs that may also have photosensitizing properties (and were indeed found to be associated with skin cancer risk in our previous meta-analysis) [14, 16]. In fact, it appears that statistical models should be adjusted at least by the presence of hypertension (or, if failing to do so, by the presence of comorbidities and the use of other drugs) in order to obliterate any alternative causal pathway and avoid residual confounding, but only a few of the included studies were able to do so (Table 2). The lack of control for hypertension was already pointed out as an important limitation by van den Born and colleagues, and we agree with them that the failure to properly adjust for the relevant covariates may raise concerns about the validity of some of the studies conducted so far [39].

Conclusions

The biologically plausible association between thiazide diuretics and skin cancer risk appears to be supported by the epidemiological evidence available to date only for SCC. This could be expected on the basis of the a priori considerations that these drugs are mostly used by older adults and seniors, and that SCC is reportedly the skin malignancy most strongly associated with exposure to UV radiation in adulthood [40, 41]. Instead, for melanoma and BCC, the amount of available data is still too limited and the studies published so far are either not well balanced (for melanoma, with one study greatly outweighing in size the other three studies) or very heterogeneous in terms of reported findings (for BCC). In light of recent evidence, it could be appropriate for the IARC to reconsider its judgement on the carcinogenicity

Table 2 Main characteristics of the studies included in the review and meta-analysis on thiazide diuretics use and skin cancer risk

Author, year	Study design	Adjusting variables	Assessment of exposure (thiazide diuretics use)
Pedersen, 2018	Case-control study, population-based, matched by age and gender (1:20 ratio)	Age, gender, school level, comorbidities (diabetes, COPD, chronic renal failure, other), CCI, use of selected drugs (photosensitizing, anti-neoplastic, NSAIDs, statins, others), alcohol use	Linkage with electronic database
Pottegård, 2018	Case-control study, population-based, matched by age and gender (1:10 ratio)	Age, gender, school level, comorbidities (diabetes, COPD, chronic renal failure, other), CCI, use of selected medications (photosensitizing, anti-neoplastic, NSAIDs, statins, others), alcohol use	Linkage with electronic database
Shaw, 2018 (conference abstract)	Secondary analysis of an RCT (use of topical 5-FU on KSC development)	Not reported	Linkage with electronic database
Nardone, 2017	Matched cohort study, users vs. non-users of thiazide diuretics matched by age and follow-up time (1:3 ratio)	Age, gender, ethnicity, CCI	Linkage with electronic database
Pottegård, 2017	Case-control study, population-based, matched by age and gender (1:100 ratio)	Age, gender, school level, comorbidities (diabetes, COPD, other), CCI, use of selected drugs (photosensitizing, anti-neoplastic, NSAIDs, statins, others), alcohol use	Linkage with electronic database
Robinson, 2013	Case-control study, population-based, frequency-matched by age and gender	Age, gender, history of sunburns	Self-reported
Friedman, 2012	Case-control study nested in a general-population cohort study, matched by age, gender, year of entry into the cohort (up to 50 controls per each case)	Smoking status; users of other anti-hypertensive drugs (triamterene, lisinopril, nifedipine and atenolol) were excluded	Linkage with electronic database
De Vries, 2012	Case-control study, hospital-based, controls from dermatology or allergy wards, matched by age and gender (ratio 1:2 for melanoma, 1:1 for KSC)	Age, gender, country, phototype	Self-reported
Ruiter, 2010	Cohort study (general population-based)	Age, gender, ethnicity, smoking status, tendency to sunburn, outdoor work, hair and eye colour, use of selected drugs (photosensitizing, anti-hypertensives, NSAIDs, statins, others)	Linkage with electronic database
Westerdahl, 1996	Case-control study, population-based, matched by age, gender, and place of residence (1:2 ratio)	Age, gender, history of sunburns, hair colour, naevi	Self-reported

CCI Charlson's Comorbidity index, COPD chronic obstructive pulmonary disease, KSC keratinocyte skin cancer, NSAIDs non-steroidal anti-inflammatory drugs, RCT randomized controlled trial

of hydrochlorothiazide, which was evaluated as possibly (group 2B, instead of probably, group 2A) carcinogenic to humans in 2016 [18•]. However, some elements suggest caution in drawing conclusions: among these, the diversity in design among studies, the scarcity of data on dose-response relationship, and the concerns about the validity of results (at least for some of the studies) due to the possibly inadequate adjustment of multivariable statistical models.

Thiazide diuretics are among the most commonly prescribed diuretics and their possible association with skin cancer risk has indisputably large public health implications. On the other side, hypertension has a far greater disease burden

than skin cancer, and thiazide diuretics are very effective anti-hypertensive drugs. Moreover, most skin cancers that could occur in hypertensive patients as a result of thiazide diuretics therapy would be of the non-melanoma type and, therefore, less life-threatening than the underlying cardiovascular disease. Therefore, it is critical to carefully weigh the pros and cons of any recommendation regarding the use of these drugs [42]. A prudent approach in the management of patients treated with thiazide diuretics could be to recommend taking precautions to reduce skin cancer risk (e.g., use of sunscreens, sunlight avoidance) and undergoing regular dermatological follow-up for early diagnosis. Critically, optimal blood pressure control must remain a priority for

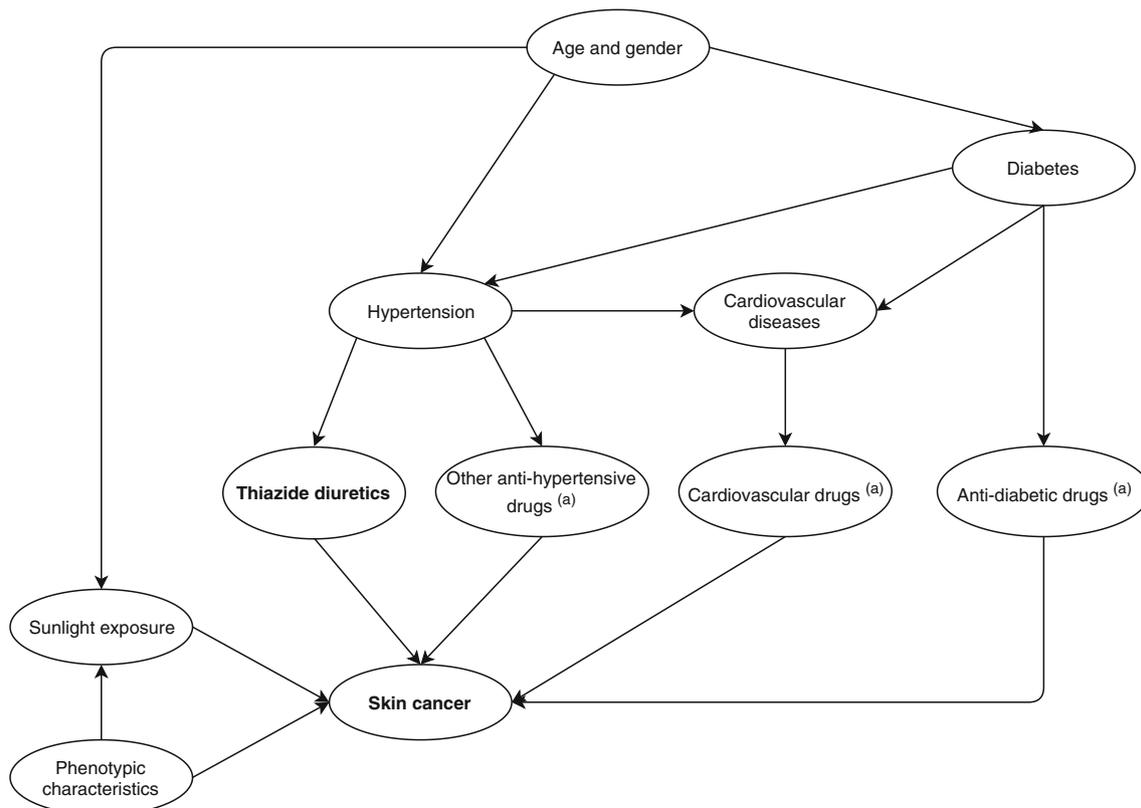


Fig. 2 Simplified directed acyclic graph conceptualizing the causal links between demographics, hypertension and common comorbidities, thiazide diuretics and other photosensitizing drugs, phenotypic

characteristics, sunlight exposure, and skin cancer. ^(a)Some drugs belonging to this group have known photosensitizing properties and/or have been reported to be associated with skin cancer risk in literature

clinicians, and should not be overlooked for any reason. Consistently with this approach, the British and Irish Hypertension Society recently recommended that thiazide-like drugs (e.g., chlorthalidone or indapamide) should be preferred over thiazide diuretics (like hydrochlorothiazide or bendroflumethiazide) and when hypertension treatment must be started, but advised not to discontinue treatment with the latter drugs in patients whose blood pressure is stable and well controlled [43•]. Likewise, the European Medicines Agency stated that hypertensive patients treated with hydrochlorothiazide should be informed about the risks, limit exposure to UV rays, and regularly check their skin, but should not stop treatment unless they previously experienced KSC [15•]. These and similar recommendations, which we fully endorse, appear acceptable for the time being, but somehow suffer from the still limited scientific evidence in the field. Therefore, we believe it important that well-designed studies are conducted in the near future focusing in particular on those aspects that are currently still controversial, such as the association with melanoma and BCC, the precise quantification of the risk and the dose-response relationship, and the interaction with other photosensitizing drugs that may be taken concomitantly with thiazide diuretics and can therefore contribute to the risk of developing a skin cancer.

Compliance with Ethical Standards

Conflict of Interest Benedetta Bendinelli, Giovanna Masala, Giuseppe Garamella, Domenico Palli, and Saverio Caini declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Recommendation on whether hydrochlorothiazide should be (1) considered to start treating patients newly diagnosed with hypertension, or (2) discontinued for patients already using it.

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