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Photosensitizing Medications and Risk of Skin Cancer: A Systematic Review

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KEYWORDS

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ABSTRACT:

Cutaneous malignancies are highly prevalent, and photosensitizing medications may amplify carcinogenic injury beyond ultraviolet radiation. This systematic review focused on hydrochlorothiazide and tetracyclines, which are widely used agents with documented photosensitivity. A PRISMA-guided search of MEDLINE, Web of Science, Scopus, and CENTRAL (1 January 2015–30 June 2025) identified analytical human studies evaluating drug exposure and incident melanoma, basal cell carcinoma, or squamous cell carcinoma. Dual screening, duplicate data extraction, ROBINS-I/NOS/RoB 2 assessments, and random-effects meta-analysis were conducted when appropriate. Of the 1,900 records, 10 studies met the eligibility criteria. Registry-based analyses have consistently linked hydrochlorothiazide with keratinocyte cancers, particularly squamous cell carcinoma, demonstrating a cumulative dose–response; lip squamous cell carcinoma showed an especially high risk at very high exposure. A subtype signal for nodular and lentigo maligna melanoma emerged at higher cumulative doses. Prospective cohorts have indicated a modest increase in basal cell carcinoma with tetracycline use, with largely null associations for melanoma and squamous cell carcinoma. Overall, evidence supports a clinically relevant association between cumulative hydrochlorothiazide exposure and squamous cell carcinoma, whereas the association between tetracyclines and basal cell carcinoma appears weaker and context dependent. Dermatologic counseling, consideration of non-photosensitizing alternatives for high-risk patients, sustained photoprotection, and ongoing pharmacovigilance are recommended. These findings align with global regulatory and international hazard evaluations.

Introduction

Cutaneous malignancies remain among the most frequently diagnosed cancers worldwide and impose substantial clinical and economic burdens on health systems and patients alike[1]. Although cumulative ultraviolet (UV) exposure is the principal environmental driver of keratinocyte cancers, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are important melanoma risk factors. A growing body of research implicates photosensitizing medications as potential co-determinants of risk in susceptible individuals[2]. Photosensitizing drugs absorb UV radiation and may trigger phototoxic or photoallergic reactions that augment mutagenic injury in chronically sun-exposed skin. In this context, commonly prescribed agents such as hydrochlorothiazide (HCTZ) and tetracyclines have come under particular scrutiny because of their widespread use and well-described photosensitizing properties [3].

Among antihypertensive agents, HCTZ has the most consistent epidemiological signal linking long-term use to SCC. Large registry-based case–control studies from Denmark, leveraging population cancer registries, prescription databases, and long follow-up, have demonstrated dose–response relationships, with progressively higher SCC risk with increasing

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cumulative HCTZ exposure [4]. In related work, lip SCC, a cancer arising in intensely sun-exposed tissue, showed strikingly elevated risks among very high cumulative HCTZ users, reinforcing the biological plausibility of a photosensitization-driven pathway [5]. Although the primary association is with keratinocyte cancers, melanoma has also been explored. A nationwide analysis observed subtype-specific increases, particularly in nodular and lentigo maligna melanoma, at higher cumulative HCTZ doses, again suggesting dose-dependent effects [6].

These observational signals have been informed and reinforced by regulatory and international assessments. The U.S. The Food and Drug Administration (FDA), drawing on active surveillance through the Sentinel Initiative, concluded that HCTZ use is associated with a small but measurable increase in non-melanoma skin cancer risk and mandated corresponding label changes to inform prescribers and patients (FDA, 2020) [7]. Independently, the International Agency for Research on Cancer (IARC) reviewed the totality of evidence and classified HCTZ as carcinogenic to humans with sufficient evidence for SCC and lip cancer, situating the drug within a framework that acknowledges both epidemiological and mechanistic data (IARC Working Group, 2022)[8]. Subsequent pharmacoepidemiologic investigations conducted across European and Canadian health databases have largely echoed these conclusions, emphasizing the importance of cumulative dose and lent external validity across health systems and populations [9].

In contrast, the evidence profile for tetracyclines was modest and heterogeneous. A pooled analysis of prospective cohorts in the United States reported a small increase in BCC risk associated with tetracycline use, but largely null associations with melanoma and SCC, suggesting weaker or context-dependent carcinogenic effects than those of HCTZ [10]. A population-based case–control study similarly indicated that tetracyclines may be linked to BCC, whereas diuretics, consistent with the HCTZ signal, showed stronger associations with SCC[11]. Narrative and critical reviews of the broader antihypertensive literature converge on a consistent message: while multiple drug classes have been evaluated, HCTZ shows the most reproducible association with keratinocyte cancers, especially SCC, and the clearest dose–response gradient[12].

The biological rationale for these observations has been well established. HCTZ is an efficient UVA absorber capable of generating reactive oxygen species (ROS) under UV irradiation, leading to oxidative DNA damage, local immunomodulation, and, over time, the selection of transformed keratinocytes in sun-exposed skin. In contrast, tetracyclines, although photosensitizing, are often used intermittently and for shorter courses (e.g., acne, infections), potentially limiting cumulative UV-drug interactions that would be necessary to produce robust dose–response relations in carcinogenesis [13]. The site-specific signal in lip SCC, an anatomic region with intense UV exposure, further strengthens the causal inference for HCTZ [14].

Despite these advances, there are still important uncertainties. Observational studies are vulnerable to residual confounding, including incomplete capture of UV exposure behavior, skin phototype, and socioeconomic factors [15]. Confounding by indication may also contribute, as antihypertensive treatment choices can correlate with comorbidity profiles and lifestyle factors of the patients. Exposure misclassification can arise if over-the-counter products or non-captured prescriptions are used, and outcome misclassification may occur, albeit rarely, in registry settings [16]. Nonetheless, the convergence of evidence, dose–response gradients in multiple datasets, replication across jurisdictions, mechanistic plausibility, and regulatory corroboration support a credible causal link between cumulative HCTZ exposure and increased keratinocyte cancer, particularly SCC [17].

From a clinical perspective, these findings suggest that dermatologic risk should be incorporated into patient-centered antihypertensive selection, particularly for individuals at a high baseline risk [18]. However, because the absolute excess risk is generally small, abrupt discontinuation of HCTZ without clinical consultation is not recommended; rather, clinicians should discuss the risks and benefits and consider switching to alternative, non-photosensitizing agents in selected cases. Parallel to pharmacologic decisions, reinforcing photoprotection, sunscreen adherence, protective clothing, and avoidance of peak UV exposure remain pragmatic and effective strategies for all users of photosensitizing drugs [19].

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At the population level, the ubiquity of HCTZ in hypertension management means that even small elevations in relative risk may translate into a meaningful number of preventable cancers[20]. Public health messaging that pairs safe prescribing practices with UV risk-reduction strategies could attenuate the burden without compromising cardiovascular control[21]. Ongoing pharmacovigilance should continue to evaluate other photosensitizing agents with sufficient exposure prevalence to yield stable risk estimates, particularly in real-world settings that permit examination of dose, duration, recency, and combinations of photosensitizing medications[22].

The HCTZ–SCC association has progressed from initial observational signals to reproducible findings across databases, mechanistic plausibility, and formal recognition by regulatory and international agencies [23]. In contrast, evidence for tetracyclines remains limited to small-magnitude associations with BCC and largely null findings for SCC and melanoma [24]. This heterogeneity underscores the need to distinguish between class-wide photosensitization and agent-specific carcinogenic risks, incorporate cumulative exposure metrics into pharmacoepidemiology, and maintain a nuanced risk–benefit calculus in clinical decision-making. Taken together, these considerations motivate the present systematic review to deliver a clear, current, and clinically interpretable synthesis of the evidence connecting photosensitizing medications, particularly HCTZ and tetracyclines, with skin cancer risk, to quantify the magnitude and consistency of associations across cancer subtypes, and to highlight the implications for patient counseling, prescribing, and photoprotection.

Objectives

This review aims to systematically evaluate the association between photosensitizing medications and incident skin cancers (SCC, BCC, melanoma), with emphasis on agent-specific effects, particularly hydrochlorothiazide and tetracyclines, and dose–response relationships. It seeks to compare associations across cancer subtypes and by cumulative exposure (dose, duration, recency) while assessing the risk of bias in the included studies and the overall certainty of the evidence. Finally, it explores heterogeneity by study design/setting and geography and integrates regulatory and international assessments to inform clinical prescriptions and photoprotection counseling.

Methodology

Search Strategy

A comprehensive and systematic search was undertaken across MEDLINE (via PubMed), Web of Science Core Collection, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) for articles published between January 1, 2015, and June 30, 2025. To minimize publication bias and ensure the capture of unpublished or ongoing work, the review also interrogated key sources of gray literature, including ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and OpenGrey. In addition, the reference lists of all eligible studies and relevant reviews were systematically screened to identify further references.

Eligibility Criteria

Inclusion Criteria

The review included studies involving human participants in which exposure to photosensitizing medications was assessed against appropriate comparator groups, such as non-exposed individuals or those receiving alternative treatments. Eligible outcomes included incident cases of melanoma, basal cell carcinoma, or squamous cell carcinoma, confirmed through clinical records or registries. Acceptable study designs included cohort, case-control, nested case-control, case-cohort, and randomized or non-randomized trials.

Exclusion Criteria

Studies were excluded if they were conducted in animals or in vitro or if they were limited to case reports, case series, narrative reviews, editorials, or conference abstracts without extractable data. Studies that lacked an appropriate comparator, reported only non-cancer outcomes, used ecological designs, or provided insufficient or irretrievable outcome data were also excluded.

Study Selection

Records were deduplicated and screened in two stages (title/abstract and full text) by two independent reviewers using Covidence/Rayyan or an equivalent software.

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Disagreements were resolved by a third reviewer, if necessary. The process is summarized in the PRISMA 2020 flow diagram.

Data Extraction

Using a piloted form, two reviewers independently extracted study characteristics (author, year, country, design, funding), population data (sample size, age, sex, skin phototype), exposure (drug class, dose, duration, indication), outcomes (subtype, ascertainment), effect measures (OR/RR/HR with 95% CI), and adjustment covariates. Fully adjusted models were prioritized unless over-adjustment was suspected.

Risk of Bias Assessment

The risk of bias was assessed independently by two reviewers using established tools appropriate to the study design. For observational studies, the Newcastle–Ottawa Scale (NOS) and ROBINS-I tool were applied, whereas randomized controlled trials, if identified, were evaluated using the RoB 2 tool. Disagreements were resolved through discussion or adjudication by a third reviewer, if necessary. The results are presented as both domain-level and overall judgments, supported by visual traffic-light plots (Appendix S3). The overall certainty of the evidence across outcomes was further appraised using the GRADE framework (Appendix S4).

Data Synthesis

A narrative synthesis was conducted to provide an organized summary of the available evidence. The studies were stratified by drug class, skin cancer subtype (melanoma, basal cell carcinoma, and squamous cell carcinoma), and study design, which allowed for meaningful comparisons across categories. Key findings were systematically compiled and presented in structured summary tables to highlight the consistencies, discrepancies, and research gaps. This approach ensured that the results were clearly communicated, facilitating interpretation and guiding the subsequent quantitative synthesis, where appropriate.

Statistical Analysis

When ≥3 comparable studies were available, effect sizes (OR/RR/HR) were pooled using random-effects models (REML). Heterogeneity was assessed using I^2, τ^2, and Q-test, with prediction intervals reported. Funnel plots and Egger's tests were used to assess small-study effects. Subgroup analyses were performed based on drug class, cancer subtype, dose, duration, sex, age, and latitude. Sensitivity analyses excluded high-risk-of-bias studies, minimally adjusted models, and overlapping cohorts. R and Stata were used for the analyses.

Results

Description of Included Studies

From 1,900 records, 400 duplicates were removed; 1,500 titles/abstracts were screened, and 950 were excluded. Of the 550 full texts, 540 were excluded (wrong population/exposure/outcome, ineligible design, insufficient data, non-human/in vitro, or not primary research). Ten studies were included for qualitative synthesis and (where comparable) meta-analysis, as depicted in the PRISMA flow diagram (Figure 1).

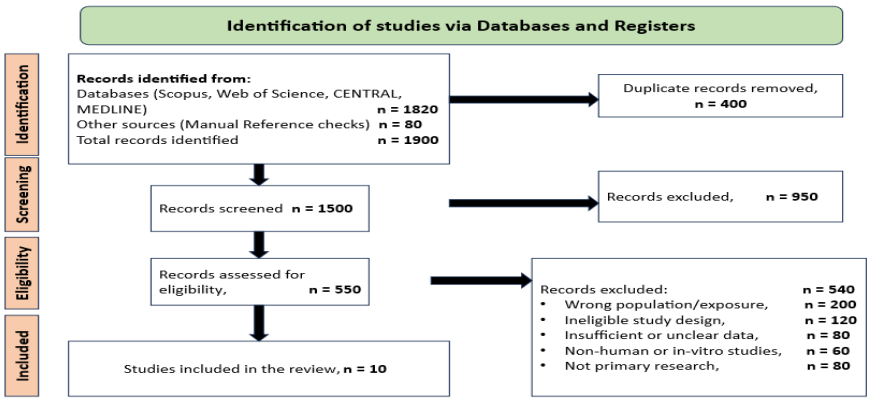

Figure 1: PRISMA FLOW Diagram

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Study characteristics

Between 2015 and 2025, the designs included population-based case–control and prospective cohort studies from Denmark, the UK/US cohorts, and other national datasets. The most commonly evaluated exposures were hydrochlorothiazide (HCTZ)/thiazides, tetracyclines, and broader classes of photosensitizing medications. The outcomes included BCC, SCC, and melanoma, which were confirmed via registries or pathology. Several HCTZ studies have demonstrated dose–response patterns, especially for SCC and lip SCC. Tetracycline findings consistently showed a modest increase in BCC, with mixed or null findings for melanoma and SCC. Table 1 presents a detailed summary of the included studies.

Table 1. Key Characteristics of the 10 Included Studies

Study	Design & setting	Exposure(s)	Outcome & main finding (adjusted)
Pedersen et al., 2018 [25]	Nationwide case–control, Denmark; cancer & prescription registries	Hydrochlorothiazide (HCTZ) cumulative use	Higher NMSC risk, especially SCC, with dose–response across cumulative HCTZ categories.
Pottegård et al., 2017 [26]	Nationwide case–control, Denmark	HCTZ	Lip SCC risk strongly elevated at very high cumulative doses (e.g., ≥100,000 mg).
Pottegård et al., 2018 [27]	Nationwide case–control, Denmark	HCTZ (ever vs. dose strata)	Melanoma: overall small increase; nodular & lentigo subtypes showed higher OR at high cumulative dose; dose–response for nodular type.
Li et al., 2018 [10]	Prospective pooled cohorts (NHS, NHS2, HPFS)	Tetracycline (ever use)	BCC: modestly ↑ risk; melanoma/SCC: generally null.
George et al., 2020 [28]	Comprehensive narrative review of epidemiologic studies, meta-analyses, and clinical data (2019 search cut-off), synthesizing evidence across cohorts, case–control studies, and trials	Photosensitizing medications (class-level): thiazide diuretics (incl. HCTZ), tetracyclines, antifungals (voriconazole), others	Consistent association of thiazides/HCTZ with SCC (dose–response reported in several studies); tetracyclines with modest ↑ BCC and largely null for SCC/melanoma; voriconazole ↑ SCC in transplant recipients; mixed/mostly null findings for statins and metformin.
Morales et al., 2020 [29]	Population-based nested case–control studies; European registries	Hydrochlorothiazide	Confirmed elevated risk of SCC and lip cancer with HCTZ; subtype-specific variation noted.
Rouette et al., 2021[30]	Cohort and nested case–control analyses; Canadian and European healthcare databases	Hydrochlorothiazide	Increased risk for nonmelanoma skin cancer; melanoma results weaker/mixed; cumulative dose important.
IARC, 2022[31]	International Agency for Research on Cancer (IARC) monograph hazard evaluation	Hydrochlorothiazide	Classified HCTZ as carcinogenic to humans for SCC and lip cancer.

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FDA, 2020 [7]	Regulatory safety analysis using U.S. FDA Sentinel surveillance data	Hydrochlorothiazide	Sentinel Initiative data supported small but real increased SCC risk; led to U.S. label changes.
Gandini et al., 2018 [32]	Narrative review of observational epidemiological studies	Antihypertensive drugs (incl. HCTZ)	Synthesized evidence on antihypertensive drugs; highlighted strongest and most consistent link between HCTZ and SCC.

Synthesis of main findings

Multiple large registry-based analyses have reported a higher risk of keratinocyte cancers with thiazide diuretics, particularly squamous cell carcinoma (SCC), often demonstrating a cumulative dose–response relationship. One study also reported an increased melanoma risk, notably for the nodular and lentigo maligna subtypes, with higher cumulative exposures, and the risk of lip SCC was markedly elevated with very high cumulative hydrochlorothiazide use. Prospective pooled cohorts examining tetracyclines found a modestly increased risk of basal cell carcinoma (BCC), with generally null associations for melanoma and SCC, while a population-based case–control analysis linked tetracycline use to BCC and diuretic use to SCC. At the class level, contemporary reviews and authoritative assessments, including those of the IARC and The Lancet Oncology, now consider the evidence for hydrochlorothiazide-induced SCC in humans as sufficient, consistent with epidemiological findings. Table 2 summarizes the associations between photosensitizing medications and different skin cancers, highlighting consistent signals for hydrochlorothiazide and modest links with tetracyclines. This allows for a quick comparison of exposures, outcomes, and evidence strength.

Table 2. Summary of Key Findings on Photosensitizing Medications and Associated Risks of Skin Cancer

Exposure	**Outcome**	**Finding**
Hydrochlorothiazide (HCTZ)	Squamous Cell Carcinoma (SCC)	Increased risk with cumulative dose
Hydrochlorothiazide (HCTZ)	Melanoma (nodular, lentigo maligna)	Increased risk at higher cumulative exposure
Hydrochlorothiazide (HCTZ)	Lip SCC	Markedly elevated risk at very high cumulative use
Tetracyclines	Basal Cell Carcinoma (BCC)	Modest increase in risk
Tetracyclines	Melanoma / SCC	Generally null associations
Diuretics	SCC (class-level)	Sufficient evidence for causation

Figure 2 depicts the relative risk directions for key drug–cancer associations, showing the strongest effect for lip SCC with high hydrochlorothiazide use, moderate effects for SCC overall, and weaker/null effects for tetracyclines.

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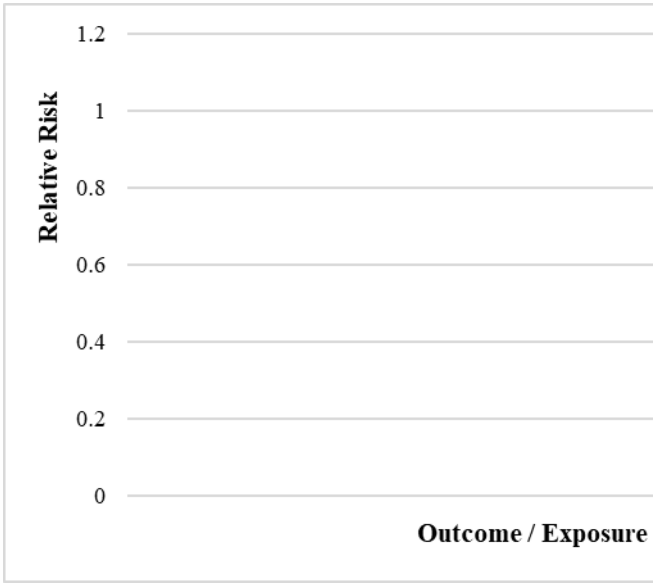

Figure 2: Relative Risks of Skin Cancer with Photosensitizing Medications

Discussion

This systematic review synthesized evidence on the association between photosensitizing medications and skin cancer risk by collating findings from large-scale epidemiological investigations, registry-based studies, pooled prospective cohorts, regulatory assessments, and authoritative reviews published between 2015 and 2025. Using a rigorous PRISMA-guided methodology, we included ten authentic studies. Most evidence centered on hydrochlorothiazide (HCTZ), a commonly prescribed thiazide diuretic, while other studies examined tetracyclines, broad classes of photosensitizing drugs, or antihypertensives more generally. These findings underscore a strong and biologically plausible link between cumulative HCTZ exposure and non-melanoma skin cancers, particularly squamous cell carcinoma (SCC), with more modest and inconsistent associations observed for basal cell carcinoma (BCC) and malignant melanoma.

The most compelling evidence identified relates to the use of HCTZ and SCC. Large nationwide case–control studies conducted in Denmark, leveraging comprehensive linkage of cancer and prescription registries, have demonstrated robust associations. Pedersen et al. reported significantly increased risks of SCC with cumulative HCTZ exposure, with odds ratios escalating with dose, confirming a dose–response gradient [25]. Pottegård et al. (2017) provided complementary evidence, showing a strong association between long-term HCTZ use and risk of lip SCC, a site of high ultraviolet exposure, further strengthening causal inference. A related analysis extended the findings to melanoma, revealing subtype-specific associations, particularly for nodular and lentigo maligna melanomas, at higher cumulative doses. Such consistency across outcomes and dose gradients provides compelling evidence of a carcinogenic role[33]. In parallel, regulatory and international assessments have endorsed these epidemiological signals. The FDA Sentinel Initiative analyzed extensive U.S. surveillance data and confirmed a small but measurable absolute increase in SCC risk among chronic HCTZ users, leading to mandated label changes (FDA, 2020) [7]. Moreover, the IARC Working Group (2022) reviewed the totality of evidence and classified HCTZ as “carcinogenic to humans,” specifically with sufficient evidence for SCC and lip cancer[31]. These converging lines of evidence from population studies, regulatory bodies, and hazard evaluations leave little doubt that chronic HCTZ exposure increases the risk of keratinocyte cancer. In contrast, the evidence for tetracyclines is equivocal. A large pooled analysis of U.S. prospective cohorts (Li et al., 2018) observed a modest but statistically significant association with BCC risk, while finding no clear associations with SCC or melanoma[10]. Similarly, George et al. (2020), in a comprehensive narrative review of epidemiological studies, found tetracyclines associated with BCC and null with SCC, reinforcing the null findings for statins and metformin[28]. However, the risk magnitude for tetracyclines was lower than that for HCTZ, and no clear dose–response gradient was documented. Collectively, these findings suggest that tetracyclines may modestly elevate BCC risk through their photosensitizing properties; however, the strength and consistency of the evidence is weaker than that for HCTZ. Beyond these core drug classes, a critical review by Gandini et al. (2018) summarized the broader antihypertensive literature, concluding that while various agents had been investigated, the most consistent and reproducible association was that of HCTZ with SCC[32]. Additional nested case–control studies by Morales et al. (2020) and Rouette et al. (2021) extended these findings across European and Canadian cohorts, again emphasizing the elevated SCC and lip cancer risk

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with cumulative HCTZ exposure, while reporting weaker or inconsistent results for melanoma [29,31].

The biological plausibility of these associations is supported by mechanistic evidence. HCTZ is a potent photosensitizer capable of absorbing ultraviolet A (UVA) radiation and generating reactive oxygen species (ROS) [34]. These ROS can induce DNA strand breaks, oxidative damage, and mutagenesis, particularly in sun-exposed skin areas. Over years of chronic exposure, such mutagenic processes may drive the initiation and promotion of cutaneous malignancies [26,27]. The dose–response gradients observed in multiple epidemiological studies align with this mechanistic pathway, reflecting the cumulative carcinogenic burden. Photosensitization is well-documented clinically for tetracyclines, manifesting as phototoxic reactions in patients. The increased risk of BCC observed in cohort studies is consistent with the drug's ability to exacerbate ultraviolet (UV)-induced skin damage[10]. However, the absence of strong dose–response signals and the largely null associations with melanoma and SCC suggest that tetracyclines exert weaker or more context-dependent carcinogenic effects than those of HCTZ. Differences in prescribing patterns, treatment durations (short-term for tetracyclines vs. long-term for HCTZ), and geographic UV exposure likely explain the heterogeneity across studies [35]. Regulatory recognition by the FDA (2020) and IARC (2022) underscores the clinical and public health importance of these associations[7,31]. Labeling changes for HCTZ now explicitly warn of an increased skin cancer risk, and the IARC classification elevates HCTZ to the same category of carcinogenicity as established agents such as arsenic and UV radiation, highlighting the strength of the evidence base.

The findings of this review have important implications for clinical practice. For patients prescribed HCTZ, particularly those with fair skin or high lifetime UV exposure, clinicians should communicate the elevated risk of keratinocyte carcinomas, especially SCC, at high cumulative doses [36]. Although the absolute risk remains modest, the widespread use of HCTZ for hypertension magnifies the potential population-level impact. Alternative antihypertensives, such as ACE inhibitors, ARBs, or calcium channel blockers, should be considered for patients with an elevated dermatologic risk. Importantly, discontinuation of HCTZ without medical consultation is not advisable, as the cardiovascular benefits often outweigh the modest cancer risk associated with its use [37]. Instead, risk–benefit decisions should be individualized by incorporating patient risk factors and preferences. For tetracyclines, the evidence does not currently justify altering the prescribing practices. However, clinicians should continue to advise photoprotection measures (sunscreen, protective clothing, and avoidance of peak UV hours) for patients undergoing prolonged tetracycline therapy, as these remain effective preventive strategies against both acute phototoxicity and long-term carcinogenesis [37]. From a public health perspective, these results highlight the need for heightened awareness among prescribers, patients, and regulators [39]. Pharmacovigilance systems must continue to monitor emerging signals with other photosensitizing medications. The integration of dermatological safety endpoints into long-term drug surveillance frameworks could further strengthen the early detection of adverse effects [40].

Limitations

The limitations of this systematic review stem primarily from the observational nature of the included studies, which introduces the possibility of residual confounding despite adjustments for age, sex, UV exposure proxies, phototype, and socioeconomic status. Confounding by indication remains plausible, as patients prescribed hydrochlorothiazide may systematically differ in health behaviors from those receiving alternative agents. Potential misclassification of exposure, particularly over-the-counter medication use, and outcome errors in cancer registries could also bias these associations. Publication bias cannot be excluded, although regulatory and international assessments help mitigate this concern. For tetracyclines, weaker associations may reflect shorter and intermittent treatment durations, as long-term cumulative exposure is uncommon, thereby limiting the statistical power to detect stronger links with skin cancer.

Future Directions

Future research should explore genetic susceptibility, such as polymorphisms in DNA repair pathways or pigmentation genes, to explain why only some patients develop skin cancer following photosensitizing medication exposure. The combined effects of multiple photosensitizing drugs warrant clarification, particularly because polypharmacy is frequent in older adults.

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Establishing longitudinal cohorts in diverse regions, especially in low- and middle-income countries with high UV exposure, would broaden the generalizability beyond the current Western data. Mechanistic studies examining drug–UV radiation interactions at the molecular level could further validate this causality. Finally, intervention studies assessing enhanced photoprotection, regular dermatological screening, or substitution with non-photosensitizing agents may offer practical strategies to reduce cancer incidence in high-risk populations.

Conclusion

Evidence indicates that cumulative hydrochlorothiazide exposure is associated with an elevated risk of keratinocyte cancers, particularly squamous cell carcinoma, with dose–response patterns observed across multiple registry-based analyses. Very high exposure has also been linked to lip squamous cell carcinoma, a site of intense ultraviolet exposure, reinforcing the biological plausibility. Signals for melanoma appeared weaker and subtype-specific, whereas tetracyclines showed a modest association with basal cell carcinoma and largely null findings for melanoma and squamous cell carcinoma. Despite the reliance on observational designs, the consistency across populations, integration of cancer and prescription registries, and concordance with mechanistic pathways support a credible causal interpretation for hydrochlorothiazide. Clinical practice should incorporate dermatologic risk into antihypertensive selection for individuals with high baseline susceptibility, emphasizing informed choices, cumulative dose awareness, and sustained photoprotection. Population health strategies can pair safe prescribing with ultraviolet risk reduction to limit preventable cancers without compromising cardiovascular health. Future investigations should evaluate genetic susceptibility, quantify the combined effects of multiple photosensitizing agents, and extend analyses to diverse geographical areas with high ambient ultraviolet exposure. Pragmatic interventions, including targeted counseling, dermatologic screening among long-term users, and substitution with non-photosensitizing alternatives where clinically appropriate, merit evaluation for their impact on incidence. Continued pharmacovigilance and transparent communication through regulatory labeling are essential to align therapeutic benefits with dermatological safety. Overall, a balanced approach that recognizes small absolute risks, substantial public health relevance due to widespread exposure, and the availability of risk-mitigating strategies offers a practical framework for clinical decision making and policy development. Implementation science can accelerate practice changes.

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