INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Antihypertensive Drugs and Cancer Risk: A Critical Reappraisal of Drug-Specific Signals, Hydrochlorothiazide-Associated Skin Cancer, Nitrosamine Impurities, and Regulatory Perspectives

Dr. Sanjeev Deshpande*

Dr. D. Y. Patil Institute of Pharmacy, Akurdi, Pune, India

ARTICLE INFO

Published: 26 Aug 2026
Keywords:
antihypertensive drugs; cancer; carcinogenicity; hydrochlorothiazide; angiotensin receptor blockers; nitrosamines; NDMA; NDEA; NDSRI; pharmaceutical impurities; pharmacovigilance; DNA adducts; LC-MS/MS; regulatory science
DOI:
10.5281/zenodo.22121511

ABSTRACT

Antihypertensive medicines are among the most widely prescribed long-term therapies and provide unequivocal reductions in stroke, myocardial infarction, heart failure, chronic kidney disease, and premature cardiovascular death. Because treatment may continue for decades, even modest potential adverse effects warrant careful evaluation. Concerns about cancer have arisen from observational associations, mechanistic hypotheses, randomized-trial analyzes, pharmacovigilance signals and, separately, the discovery of carcinogenic nitrosamine impurities in selected pharmaceutical products. These observations should not be confused. This critical review distinguishes three fundamentally different scenarios: intrinsic carcinogenicity of the active pharmaceutical ingredient; molecule-specific biological associations, particularly hydrochlorothiazide (HCTZ)-associated cutaneous cancer; and product-specific carcinogenic risk arising from pharmaceutical impurities such as Possible spelling mistake found. (CDMA), Possible spelling mistake found. (NDEA) and nitrosamine drug-substance-related impurities (Doris). Randomized evidence involving hundreds of thousands of participants has not demonstrated a consistent clinically important increase in overall cancer attributable to ACE inhibitors, angiotensin receptor blockers, blockers or thiamine diuretics. Observational signals for calcium-channel blockers and some Arms remain heterogeneous and vulnerable to confounding. HCTZ is different: cumulative exposure has been associated with non-melanoma skin cancer, particularly squamous-cell carcinoma, with photosensitization providing biological plausibility. The Valsartan–NDMA episode represents a pharmaceutical-quality problem rather than evidence that the ARB class is intrinsically carcinogenic. Nitrosamines can undergo metabolic activation to DNA-reactive intermediates, making analytical detection and manufacturing control essential. The review integrates Possible spelling mistake found., pharmaceutical chemistry, toxicology, analytical science, and regulatory perspectives

***Corresponding Author:** Dr. Sanjeev Deshpande
Address: *Dr. D. Y. Patil Institute of Pharmacy, Akurdi, Pune, India.*
Email ✉: svdesh3320@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

and proposes a product- and batch-aware framework for future cancer-safety investigations.

INTRODUCTION

Hypertension is a major modifiable determinant of cardiovascular, cerebrovascular and renal disease. The clinical benefit of antihypertensive therapy is firmly established, and treatment reduces major cardiovascular events and premature mortality. Nevertheless, antihypertensive exposure commonly extends over many years, making the evaluation of uncommon or delayed adverse outcomes scientifically and clinically relevant. Cancer concerns surrounding antihypertensive therapy have emerged from several evidence streams that answer different questions. Observational studies may identify statistical associations but remain vulnerable to confounding, treatment selection and reverse causation. Randomized trials provide stronger protection against confusion but may have limited duration for outcomes with long latency. Mechanistic studies can establish biological plausibility without proving clinical causality. Pharmaceutical-quality investigations address yet another question: whether a finished product contains a carcinogenic impurity generated during synthesis, formulation, storage, or other stages of manufacture. The controversy became especially prominent after the identification of NDMA in selected Alsatian products in 2018, followed by recognition of other nitrosamines in certain medicines. The pharmacological properties of Alsatian and the toxicological properties of NDMA are therefore separate issues. A second, independent signal concerns HCTZ, a photosensitizing diuretic for which epidemiological evidence has accumulated for selected skin cancers. Accordingly, this review uses a three-pathway framework: (1) intrinsic active-drug effects; (2) molecule-specific biological effects such as HCTZ-associated skin cancer; and (3) product-specific impurity-mediated risk. This distinction is central to rational pharmacovigilance and avoids the scientifically imprecise proposition that antihypertensive medicines as a therapeutic class are carcinogenic.

2. Three Distinct Cancer-Risk Scenarios

Scenario	Example	Principal mechanism	Interpretation
Intrinsic API carcinogenicity	Hypothetical carcinogenic antihypertensive	Direct molecular/genotoxic effect	Requires consistent clinical and mechanistic evidence
Molecule-specific biological effect	Hydrochlorothiazide	Photosensitization plus ultraviolet-associated damage	Epidemiological signal with biological plausibility
Pharmaceutical impurity	NDMA-contaminated valsartan product	Metabolic activation and DNA alkylation	Product/batch-specific exposure; strong toxicological basis
Confounding-associated signal	Some observational ARB/CCB associations	Age, comorbidity, indication, healthcare use and other factors	Association alone does not establish causality

3. Evidence from Randomized and Contemporary Observational Studies

An individual-participant-data meta-analysis of 33 randomized trials involving 260,447 participants and 15,012 cancer events found no consistent increase in overall cancer associated with ACE inhibitors, ARBs, β-blockers, or thiazides. A small association for calcium-channel blockers emerged in active-comparator analyses but was not statistically significant when compared with placebo. This distinction illustrates why

comparator selection is critical in drug-safety research.

More recent real-world evidence remains broadly consistent with the absence of a clinically meaningful class-wide cancer effect. A 2025 cohort study of 270,320 newly diagnosed patients with hypertension, with a median follow-up of 7.7 years and 14,264 cancer events, found no significant association of ACE inhibitors, ARBs, β-blockers, or thiazide diuretics with overall cancer. CCBs showed a modest association (HR 1.05, 95% CI 1.01–1.09), but the association disappeared in sensitivity analyses excluding short follow-up, supporting caution about residual confounding and reverse causation. These data do not prove that every antihypertensive molecule is completely free of carcinogenic potential. Rather, they argue strongly against treating antihypertensive therapy as a homogeneous carcinogenic exposure. Drug-specific analyses, exposure duration, cancer subtype, comparator selection, and latency remain essential.

4. Drug-Class-Specific Evidence

4.1 ACE Inhibitors

ACE inhibitors reduce angiotensin II generation and increase bradykinin availability. Because the renin–angiotensin system participates in angiogenesis, inflammation, vascular remodeling and cellular signalling, theoretical relationships with tumour biology have been proposed. Angiotensin II can influence oxidative stress, inflammatory signalling, vascular endothelial growth factor, proliferation and angiogenesis. However, mechanistic activity within a signalling pathway does not establish carcinogenicity of a drug. Available randomized evidence does not demonstrate an overall cancer excess attributable to ACE inhibitors.

4.2 Angiotensin Receptor Blockers

ARBs became central to the cancer debate for two different reasons: hypotheses concerning RAAS biology and the discovery of nitrosamines in selected products. Randomized evidence has not demonstrated convincing intrinsic class-wide carcinogenicity. The valsartan episode is best understood as a pharmaceutical-quality event in which manufacturing chemistry and product-specific contamination created an exposure to a potentially carcinogenic impurity.

4.3 β-Blockers

β-adrenergic signalling influences angiogenesis, inflammation, immune regulation and cellular migration, generating hypotheses about tumour biology. Nevertheless, randomized evidence does not show a consistent increase in overall cancer among β-blocker users. Continued surveillance is appropriate because of the very large population exposure, but current evidence does not justify classifying β-blockers as carcinogens.

4.4 Calcium-Channel Blockers

CCBs have generated periodic observational signals involving overall and site-specific cancer outcomes. The randomized individual-participant analysis identified a small active-comparator association, whereas placebo comparisons did not demonstrate a statistically significant excess. Contemporary cohort evidence similarly suggests that any association is modest and sensitive to follow-up and analytic choices. CCBs therefore represent an area for continued research rather than an established carcinogenic class.

4.5 Thiazide and Thiazide-Like Diuretics

Thiazide diuretics should not be treated as pharmacologically or epidemiologically interchangeable. HCTZ has a substantially

stronger skin-cancer signal than several other thiazide or thiazide-like agents. Evidence for indapamide and bendroflumethiazide is more limited or heterogeneous, and the available literature does not support assuming a class effect identical to HCTZ.

5. Hydrochlorothiazide and Skin Cancer

HCTZ is photosensitizing, providing a plausible pathway linking cumulative exposure to ultraviolet radiation and cutaneous carcinogenesis. The proposed sequence is: HCTZ exposure → cutaneous photosensitization → UV exposure → photochemical excitation → reactive oxygen species and DNA damage → mutagenesis → keratinocyte carcinogenesis.A 2022 systematic review and meta-analysis involving approximately 17.85 million participants reported associations between HCTZ and non-melanoma skin cancer, squamous-cell carcinoma and melanoma, with stronger signals for high cumulative exposure and SCC. Geographic and population heterogeneity was substantial, and the evidence for some outcomes was weaker than for SCC. A later systematic review likewise found associations across several antihypertensive categories but graded much of the evidence as low or very low quality. The most defensible interpretation is therefore molecule-specific: HCTZ has a clinically relevant epidemiological association with selected cutaneous malignancies, particularly SCC, supported by a plausible photosensitization mechanism. This should not be generalized automatically to every thiazide or thiazide-like diuretic.

6. Nitrosamine Impurities: A Pharmaceutical-Quality Problem

Nitrosamine contamination represents a fundamentally different pathway from intrinsic API carcinogenicity. Selected valsartan, losartan and other products were found to contain NDMA, NDEA or related impurities. Importantly, contamination depended on manufacturing route, process conditions, materials and batches rather than being a universal property of the ARB class.

Nitrosamines can arise through nitrosation of suitable amines in the presence of nitrosating species. Potential contributors include secondary or tertiary amines, nitrite-containing materials, contaminated raw materials, recovered solvents, recycled materials, cross-contamination, formulation conditions, storage and API-specific structural features. NDSRIs are especially challenging because they are structurally related to the API and may lack extensive compound-specific carcinogenicity data.

The toxicological pathway is well established in principle: nitrosamine exposure → absorption → metabolic activation, often involving cytochrome P450 enzymes → reactive alkylating intermediates → DNA adduct formation → replication errors and mutational accumulation → potential clonal expansion and carcinogenesis. The presence of a nitrosamine impurity therefore creates a chemically credible hazard, while actual human risk depends on concentration, exposure duration, metabolism and other determinants.

7. Regulatory and Analytical Science

The U.S. FDA's September 2024 revised guidance distinguishes small-molecule nitrosamines from NDSRIs and recommends risk assessment, testing and controls to prevent or reduce unacceptable nitrosamine levels. FDA's current acceptable-intake framework uses compound-specific data, read-across and the predicted carcinogenic potency categorization approach, with updates continuing as new scientific information becomes available.

Analytical control should combine sensitive targeted quantification with broader screening where appropriate. GC-MS and GC-MS/MS remain useful for volatile nitrosamines; LC-MS/MS supports targeted analysis of a broad range of compounds; LC-HRMS and QTOF-MS are useful for suspect and non-targeted screening, particularly for less-characterized NDSRIs. Stable-isotope-labelled internal standards are preferred where available.

A robust workflow can be expressed as: sample extraction → internal standardization → chromatographic separation → MS/MS or HRMS detection → calibration → recovery and precision assessment → limit-of-quantification determination → matrix-effect evaluation → retention-time and ion-ratio confirmation. Analytical methods should be appropriately validated for the intended matrix and concentration range.

Technique	Principal application	Strength	Limitation
GC-MS/MS	Volatile nitrosamines and confirmation	High selectivity	Less suitable for nonvolatile NDSRIs
LC-MS/MS	Targeted nitrosamine quantification	Sensitive and selective	Matrix effects require control
LC-HRMS	NDSRI and suspect screening	Accurate mass; broad coverage	Complex and relatively expensive
QTOF-MS	Suspect/non-targeted screening	Broad detection capability	Quantification may require additional validation
Stable-isotope dilution MS	Accurate quantification	High analytical accuracy	Isotope standards may be costly

8. Epidemiological Bias and Interpretation

Potential bias/ confounder	Why it matters
Age	Both hypertension treatment and cancer incidence increase with age.
Smoking	Strongly associated with cardiovascular disease and multiple cancers.
Obesity and diabetes	Influence both hypertension and cancer risk and may affect treatment choice.
UV exposure	Critical confounder/modifier in HCTZ-associated skin cancer.
Disease severity	Determines treatment selection and may correlate with cancer risk.
Polypharmacy	Makes individual-drug effects difficult to isolate.
Healthcare utilization	Greater medical contact increases cancer detection.
Drug switching	Can cause exposure misclassification.
Reverse causation	Undiagnosed cancer may alter treatment or healthcare use.
Geographic variation	Sun exposure, skin phenotype and prescribing patterns vary geographically.

Cancer outcomes should not be pooled indiscriminately. Overall cancer, melanoma, basal-cell carcinoma and squamous-cell carcinoma are biologically and epidemiologically distinct endpoints. Relative risks should also be interpreted alongside absolute risks, because a modest relative increase may correspond to a small absolute change in a low-baseline-risk population.

9. Integrated Cancer-Safety Decision Framework

A useful framework for a future signal is: epidemiological association → consistency assessment → biological plausibility → dose-response evaluation → pharmaceutical-impurity assessment → integration of randomized and

observational evidence → long-term pharmacovigilance → integrated risk–benefit assessment. Where an impurity is identified, exposure reconstruction should be product- and batch-specific whenever feasible.

The most informative future databases would connect patient, prescribed product, batch, manufacturer, API supplier, manufacturing route and measured impurity profile. This would substantially improve exposure classification and allow epidemiological studies to distinguish API effects from impurity-mediated effects.

10. Future Research Directions

Future studies should combine pharmacoepidemiology with pharmaceutical chemistry and molecular toxicology. Priorities include batch-level exposure reconstruction; high-resolution mass-spectrometric screening; DNA-adduct analysis; cancer mutational signatures; biomarker-based exposure assessment; long-term cancer registries; and mechanistic studies of NDSRI formation. Quasi-experimental analyses of treatment switching may be informative for HCTZ, provided that clinical reasons for switching are carefully addressed.

Discipline	Priority contribution
Pharmaceutical chemistry	Process chemistry, reaction-pathway prediction and impurity profiling
Analytical chemistry	LC-MS/MS, LC-HRMS, GC-MS/MS and isotope-dilution methods
Toxicology	Mutagenicity, genotoxicity and DNA-adduct assessment
Molecular biology	DNA repair, oxidative stress and mutational signatures
Epidemiology	Long-term cohorts and cancer registries
Pharmacoepidemiology	Product- and batch-specific exposure reconstruction
Regulatory science	Acceptable-intake modelling, mitigation and risk management
Clinical medicine	Individualized benefit–risk assessment
Artificial intelligence	Prediction of nitrosatable structures and impurity-formation pathways

11. Limitations of the Review

The evidence base is heterogeneous, particularly for observational cancer outcomes. Many studies cannot reconstruct exact product batches or impurity concentrations, limiting direct exposure assessment. Cancer latency may exceed the follow-up of some cohorts. HCTZ studies are particularly vulnerable to differences in UV exposure, skin phenotype, and healthcare utilization. Regulatory acceptable-intake values are risk-management levels and should not be interpreted as absolute biological thresholds below which carcinogenic activity is impossible. Finally, nitrosamine regulatory recommendations continue to evolve and should be checked immediately before manuscript submission.

12. Clinical and Regulatory Implications

First, antihypertensive therapy should not be broadly characterized as carcinogenic. Second, HCTZ warrants molecule-specific attention, particularly in relation to cumulative exposure and cutaneous SCC, together with appropriate skin surveillance and sun-protection advice where clinically appropriate. Third, nitrosamine contamination should be regarded primarily as a pharmaceutical-quality and manufacturing-control issue. Fourth, cancer signals should be interpreted at the level of the individual molecule, product, exposure and mechanism. Fifth, patients should not abruptly discontinue antihypertensive therapy because of cancer concerns; medication changes should be discussed with a healthcare professional.

CONCLUSION

The proposition that the totality of current evidence does not support antihypertensive medicines as a therapeutic class causing cancer. Randomized evidence involving hundreds of thousands of participants does not demonstrate a consistent increase in overall cancer attributable to ACE inhibitors, ARBs, β-blockers, or thiazide diuretics. Observational signals involving CCBs and ARBs remain heterogeneous and are vulnerable to confounding, comparator selection, exposure misclassification, and reverse causation.

HCTZ represents an important molecule-specific signal. Its photosensitizing properties provide biological plausibility for cutaneous carcinogenesis, and multiple epidemiological studies associate cumulative exposure with SCC and other skin cancers. This evidence warrants continued pharmacovigilance and clinically appropriate risk management, but should not automatically be extrapolated to all thiazide or thiazide-like diuretics. Nitrosamine contamination represents a different problem: carcinogenic hazard can reside in a contaminant introduced or generated during pharmaceutical manufacture rather than in the pharmacological activity of the antihypertensive API. The valsartan experience demonstrated the importance of process chemistry, impurity profiling, analytical surveillance, and regulatory control. Nitrosamines can generate DNA-reactive metabolites, making exposure limits and robust analytical controls essential. Overall, cancer safety should be evaluated at the molecular, product, batch, and exposure levels rather than by therapeutic class alone. A multidisciplinary approach integrating pharmacoepidemiology, pharmaceutical chemistry, analytical science, toxicology and regulatory science offer the most reliable path for distinguishing genuine drug-related carcinogenicity from impurity-mediated risk and residual confounding.

REFERENCES

1. Battistoni A, Tocci G, Coluccia R, et al. Antihypertensive drugs and the risk of cancer: a critical review of available evidence and perspective. J Hypertens. 2020; 38:1005–1015. doi:10.1097/HJH.0000000000002379.
2. Sanidas E, Velliou M, Papadopoulos D, et al. Antihypertensive drugs and risk of cancer: between Scylla and Charybdis. Am J Hypertens. 2020; 33:1049–1058. doi:10.1093/ajh/hpaa098.
3. Copland E, Canoy D, Nazarzadeh M, et al. Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis. Lancet Oncol. 2021; 22:1484–1494. Doi: 10.1016/S1470-2045(21)00333-4.
4. Sipahi I. Risk of cancer with angiotensin-receptor blockers increases with increasing cumulative exposure: meta-regression analysis of randomized trials. PLoS One. 2022; 17:e0263461. doi:10.1371/journal.pone.0263461.
5. Yu H, Liu Z, Wu Y, et al. Antihypertensive medications and cancer risk: evidence from 0.27 million patients with newly diagnosed hypertension. Front Pharmacol. 2025; 16:1559604. doi:10.3389/fphar.2025.1559604.
6. Wang S, Xie L, Zhuang J, et al. Association between use of antihypertensive drugs and the risk of cancer: a population-based cohort study in Shanghai. BMC Cancer. 2023; 23:425.
7. Pottegård A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med. 2017; 282:322–331.
8. Shin D, Lee ES, Kim J, et al. Association between the use of thiazide diuretics and the risk of skin cancers: a meta-analysis of observational studies. J Clin Med. 2019.
9. Shao SC, Lai CC, Chen YH, et al. Associations of thiazide use with skin cancers: a systematic review and meta-analysis. BMC Med. 2022; 20:228. DOI: 10.1186/s12916-022-02419-9.

10. Andrade ACM, Felix FA, França GM, et al. Hydrochlorothiazide use and risk of cutaneous and lip squamous cell carcinoma: systematic review and meta-analysis. Eur J Clin Pharmacol. 2022;78:919–930.
11. Götzinger F, Wilke T, Hardtstock F, et al. Association of hydrochlorothiazide treatment compared with alternative diuretics with overall and skin cancer risk: a propensity-matched cohort study. J Hypertens. 2023;41:926–933.
12. Hashizume H, Nakatani E, Sasaki H, Miyachi Y. Hydrochlorothiazide increases risk of nonmelanoma skin cancer in an elderly Japanese cohort with hypertension: the Shizuoka study. JAAD Int. 2023;12:49–57.
13. Birck MG, Moura CS, Machado MAA, et al. Skin cancer and hydrochlorothiazide: novel population-based analyses considering personal risk factors including race/ethnicity. Hypertension. 2023;80:2218–2225.
14. Yang ASH, Djebarri L, Lee CN, et al. Hydrochlorothiazide use and risk of skin cancer: population-based retrospective cohort study. Pharmacoepidemiol Drug Saf. 2024;33:e70027.
15. Rasmussen AA, Buus NH, Steffensen SGC. Geographical differences in hydrochlorothiazide-associated risk of skin cancer. Am J Hypertens. 2024;37:924–932.
16. Cohen OG, Taylor M, Mohr C, et al. Antihypertensive medications and risk of melanoma and keratinocyte carcinomas: a systematic review and meta-analysis. JID Innov. 2024;4:100272.
17. Pottegård A, Kristensen KB, Ernst MT, et al. Use of NDMA-contaminated valsartan products and risk of cancer: Danish nationwide cohort study. BMJ. 2018;362:k3851. doi:10.1136/bmj.k3851.
18. Gomm W, Röthlein C, Bowl K, et al. N-nitrosodimethylamine-contaminated valsartan and the risk of cancer: a longitudinal cohort study based on German health insurance data. Dtsch Arztebl Int. 2021;118:357–362.
19. Eworuke E, et al. Exposure to valsartan products containing nitrosamine impurities in the United States, Canada and Denmark. Pharmacoepidemiol Drug Saf. 2024.
20. Horne J, et al. Regulatory experiences with root causes and risk factors for nitrosamine impurities in pharmaceuticals. J Pharm Sci. 2023;112:1166–1182. doi:10.1016/j.xphs.2022.12.022.
21. Bhirud D, Agrawal G, Shah H, et al. Nitrosamine impurities in pharmaceuticals: an empirical review of their detection, mechanisms, and regulatory approaches. Curr Top Med Chem. 2024;24:503–522.
22. Analytical methodologies to detect N-nitrosamine impurities in pharmaceutical products. Chem Res Toxicol. 2024. doi:10.1021/acs.chemrestox.4c00234.
23. U.S. Food and Drug Administration. Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry. Revised September 2024.
24. U.S. Food and Drug Administration. Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities. FDA; 2023, with subsequent updates.
25. U.S. Food and Drug Administration. CDER Nitrosamine Impurity Acceptable Intake Limits. Updated July 2026.
26. International Council for Harmonisation. ICH M7(R2): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Geneva: ICH; 2023.
27. International Council for Harmonisation. ICH Q9(R1): Quality Risk Management. Geneva: ICH; 2023.
28. World Health Organization. Guideline for the Pharmacological Treatment of Hypertension in Adults. Geneva: WHO; 2021.

HOW TO CITE: Dr. Sanjeev Deshpande, Antihypertensive Drugs and Cancer Risk: A Critical Reappraisal of Drug-Specific Signals, Hydrochlorothiazide-Associated Skin Cancer, Nitrosamine Impurities, and Regulatory Perspectives, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 4463-4470. https://doi.org/10.5281/zenodo.22121511