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# Review: A Pharmacovigilance Study on Risk of Cancer and Antihypertensive Drugs

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**A B S T R A C T**

The decrease in cardiovascular disease mortality is largely due to effective treatment and secondary prevention therapies. Long-term medications are increasingly used, particularly for hypertension, which requires lifelong treatment. Recent evidence has highlighted the risk of cancer associated with long-term anti-hypertensive therapy use. However, there are no definitive answers and further studies are needed to address this crucial patient safety issue.

Keywords: cancer, cancer risk, anti-hypertensive

## 1. Introduction

The two most common causes of death and morbidity in affluent countries are cardiovascular and neoplastic disorders. These conditions frequently coexist in one person, making treatment more difficult to administer and creating the possibility that there are common pathophysiological pathways connecting cancer and cardiovascular disease (CVD). Three events in 2017 brought attention to the suspected carcinogenic potential of some anti-hypertensive medications: the US Food and Drug Administration withdrew popular anti-hypertensive medications due to potentially carcinogenic byproducts; trials from Scandinavia suggested thiazide diuretics may be involved in skin neoplasms; and one trial suggested angiotensin-converting enzyme (ACE) inhibitors may be involved in lung cancer. These incidents dominated medical pages and doctor-patient contacts, causing widespread alarm among medical professionals and patients.Since its inception in the first part of the 20th century, the discussion has been enhanced by data primarily gathered from cohort studies and national registers, with randomized controlled trials (RCTs) being used only in exceptional circumstances. The validity of the evidence in this context has been compromised by the inconsistent data gathering. This article offers a critical assessment of the data pertaining to the carcinogenic potential of ACE inhibitors, diuretics, and angiotensin receptor blockers (ARBs) in particular circumstances.

### *1.1 Anti-hypertensive Anticancer Risk*

#### *1.1.1 Diuretics*

Diuretics are typically used as anti-hypertensive drugs, frequently in conjunction with other therapy, and renal cancer is a difficult issue. Since the 1980s, thiazides have been the subject of increased research, as it can be challenging to determine the overall negative impact of a single diuretic. These medications have the potential to be carcinogenic due to their toxic and mutagenic effects at the distal tubule level after prolonged exposure. It has been suggested that the poisonous metabolites of loop diuretics and thiazides, specifically N-nitroso derivatives, cause tumors.

An inadequate evaluation of risk variables and various cut-offs or methods for diagnosing hypertension are common sources of data on renal cancer in observational studies and retrospective analyses. Diabetics may, however, raise the chance of developing renal cell carcinoma by two to four times, especially in women, according to the majority of cohort and population studies conducted on humans. According to a recent meta-analysis, metabolic and neuro-hormonal pathways such the rein-angiotensin-aldosterone system, catecholamines, and vasopressin all support the link between hypertension and kidney cancer. The latest data comes from a comprehensive evaluation of 27 observational studies, which discovered a strong correlation between the use of diuretics and the risk of kidney cancer. This correlation increased with treatment duration and persisted even when smoking and hypertension were taken into account.

#### *1.1.2 Skin Cancer*

The link between diuretic use and skin cancer has been suggested for some time, especially due to the increasing incidence of cutaneous melanoma and non-melanoma skin cancers. Risk factors for skin cancer development include exposure to ultraviolet light, fair skin, light eye and hair color, and freckles. However, most available trials have not assessed these factors, and the time between exposure and skin cancer development appears too short for

biological validity. Diuretics, particularly thiazides, are photosensitizers, causing DNA damage and chronic inflammation. Self-reported consumption of diuretics, including thiazides, was associated with an increased risk of basal cell carcinoma (BCC) in a US population-based cohort study.

An observational research conducted in 2008 discovered that users of amiloride alone or in combination with hydrochlorothiazide had an elevated risk of squamous cell carcinoma and malignant melanoma. Users of sulphonamides and other low-ceiling diuretics also had an increased risk of malignant melanoma. A case control study conducted in 2015 revealed that the usage of diuretics for an extended period of time, whether alone or in conjunction with low-ceiling diuretics, was linked to an elevated risk of SCC. A dose-response connection between hydrochlorothiazide usage and BCC and SCC, particularly the latter cancer form, was observed in a recent case control study. The percentage of skin cancers linked to the use of hydrochlorothiazide was 9.0% for SCC and 0.6% for BCC; this percentage was greater in individuals under 50 years old and in women than in males. Neither indapamide nor chlorthalidone were associated with this increased risk.

Users of thiazides had a non-significant 30% higher risk of developing skin cancer, according to a recent meta-analysis of 19 research spanning the years 1993 to 2016 on the use of diuretics and the risk of skin cancer. Based on the existing epidemiological data, thiazide diuretics and the risk of SCC appear to be associated. The British and Irish Hypertension Society suggested that when beginning hypertension treatment, thiazide-like medications (such as chlorthalidone or indapamide) should be chosen over thiazide diuretics (such as hydrochlorothiazide or bendroflumethiazide). However, patients with well-controlled blood pressure levels shouldn't stop taking these medications.

#### *1.1.3 Renin Angiotensin Aldosterone System Blockers*

The US FDA withdrew approval for many ARBs, including valsartan, irbesartan, and losartan, because they included nitrogen compounds that were known to have carcinogenic potential. These contaminants were introduced when active principles were processed in China and India, which helped to establish the carcinogenicity of ARBs. Numerous cancer forms exhibit type I angiotensin II receptors, indicating the complicated function that angiotensin and its receptors play in the genesis of cancer. Vascular endothelial growth factor expression is decreased and matrix metalloproteases are inhibited as part of the anti-tumor effect of ACE inhibitors and ARBs. It is unclear, therefore, what part persistent overstimulation of type II angiotensin receptors and the rise in renin levels brought on by blocking type I angiotensin II During ARB medication, there may be an anti-angiogenic impact on tumors due to the rise in angiotensin.

A 2011 meta-analysis by Sipahi et al. found that antiretroviral drugs (ARBs) were associated with a marginal increase in new cancer diagnoses, primarily lung and prostate cancers, when compared to the control group. Studies with a one-year follow-up were also included in the meta-analysis, even though the longest follow-up duration was five years. The Renal Outcomes with Telmisartan, Ramipril, or Both in People at High Vascular Risk (ONTARGET) trial was the primary driver of the outcomes. A more detailed analysis of individual data from fifteen multi center double-blind clinical trials involving over one thirty thousand persons at high cardiovascular risk, compared to control, showed no increase in cancer risk overall or site-specific from specific ARBs.receptors play.

A statewide retrospective observational research conducted in the United States with over 1 million controls and 70,000 cases ruled out any correlation between ARB medication and lung cancer. A minor absolute risk decrease of 0.30 lung malignancies per 1,000 person-years was seen in the ARB-treated group, suggesting that ARB usage had a preventive effect. When comparing an ARB with a placebo, an ARB with an ACE inhibitor, an ARB with partial usage of ACE inhibition with a placebo plus partial use of ACE inhibition, or an ARB in conjunction with an ACE inhibitor, a recent meta-analysis of 19 RCTs revealed no significant changes.

In the ACE inhibitor group, the study identified no significant correlation between smoking status and cancer risk, while in the non-smoker group, there was no correlation between ARB-based medication and cancer. In certain populations, the length and intensity of smoking were not completely evaluated. Although there is currently little concrete evidence, persistent cough, a typical side effect of ACE inhibitors, may be the result of detection bias.

## 2. Conclusion

Over the past 50 years, the potential carcinogenic effects of drugs, foods, and lifestyles have gained significant scientific attention. Recent data on the role of diuretics, ARBs, and ACE inhibitors in promoting cancer development highlights the difficulty in obtaining reliable evidence in this setting. Observational studies often present biases, making 'big data' collection more in-depth necessary for evidence-based recommendations. Currently, recommendations to interrupt successful anti hypertensive therapies to avoid a generic cancer risk are not justified. Instead, watchful waiting and attention to patients with increased cancer risk is the best strategy.

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