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Effects of ACE inhibitors/ARBs on lung cancer; an updated mini-review on recent data

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Abstract
Several observational studies have indicated a potential protective effect of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) against lung cancer. These investigations have demonstrated a reduced risk of lung cancer among individuals utilizing ACEIs or ARBs compared to those not receiving these medications. However, it is crucial to acknowledge that observational studies cannot establish a cause-and-effect relationship, as other confounding factors may be at play. Conversely, conflicting outcomes have been reported in certain studies, revealing no discernible association between ACEIs/ARBs and the risk of lung cancer. Furthermore, limited evidence from randomized controlled trials specifically designed to investigate this relationship exists. It is imperative to recognize that these trials have inherent limitations, including potential biases and confounding factors. Therefore, additional research is essential to ascertain a definitive connection between ACEIs/ARBs and lung cancer. This review seeks to assess the available data and explore potential mechanisms underlying this association.

Keywords: Lung cancer, ACE inhibitors, Pulmonary cancer, Renin-angiotensin system, Angiotensin receptor blockers, Angiotensin-converting enzyme inhibitors

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Introduction

Angiotensin receptor blockers (ARBs) are widely recognized pharmaceuticals utilized for the management of hypertension. They function by inhibiting the action of angiotensin II on its receptors, thereby contributing to the regulation of blood pressure (1). Angiotensin receptor blockers have gained widespread prescription owing to their favorable safety profile and numerous cardiovascular benefits (2). Angiotensin-converting enzyme inhibitors (ACEIs) have long been utilized as a first-line therapy for high blood pressure management and cardiovascular protection.

The primary mechanism of action for angiotensin receptor blockers is centered on inhibiting the conversion of angiotensin I to angiotensin II. This ultimately results in diminished vasoconstriction, contributing to the lowering of blood pressure (3). However, recent studies suggest that long-term administration of ACEIs/ARBs may be accompanied by a strengthened risk of certain cancers, potentially exerting a cancer-enhancement effect. These compounds are commonly prescribed for various cardiovascular conditions, and their benefits in managing these conditions generally outweigh any potential risks (4). It is essential to acknowledge that the risk of developing pulmonary malignancy is influenced by various factors, encompassing tobacco smoking and exposure to environmental pollutants. This review seeks to examine the existing evidence concerning the potential impact of ACEIs and ARBs on cancer, specifically exploring the possible enhancement or protective efficacy of these medications in the context of cancer development (5).

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including; pulmonary cancer, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, lung cancer, ACE inhibitors, cancer, tumorigenesis, progression, angiogenesis, apoptosis, immune response, renin-angiotensin system, hypertension, cardiovascular diseases and lung cancer

Results of the literature review

In a cohort of 992 061 individuals recently treated with

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Implication for health policy/practice/research/ medical education

The existing body of evidence concerning the correlation between angiotensin receptor blockers (ARBs)/angiotensin-converting enzyme inhibitors and lung cancer is constrained. Several studies propose a plausible protective influence of these medications against lung cancer; however, conflicting outcomes and a lack of significant associations have been reported in other investigations. The current available evidence does not provide conclusive findings, underscoring the necessity for further research to elucidate a definitive connection between these pharmaceutical agents and the occurrence of lung cancer.

antihypertensive agents, Hicks et al showed 7952 cases of events per 1000 person-years (in a mean followed for 6.4 ± 4.7 years). Overall, administration of ACEIs was linked to a strengthened risk of pulmonary malignancy, compared with administration of ARBs. They showed hazard ratios gradually raised with longer durations of administration (6).

In another study, Moon et al assessed the risk of pulmonary cancer in association with the administration of ARBs in patients with high blood pressure in the Korean population. In a cohort comprising 60 469 individuals with a median follow-up period of 7.8 years, approximately 476 cases of pulmonary cancer were identified. The use of ARBs demonstrated a protective effect against lung tumors when compared with calcium channel blockers. This effect was particularly notable in female patients without chronic obstructive pulmonary disease, as well as in women patients without chronic obstructive pulmonary disease. They showed that the overall protective consequences of ARBs on pulmonary cancer risk remained consistent. They accordingly concluded that the ARBs could decrease the risk of pulmonary malignancy (7).

The recent study by Kristensen et al in a Danish population, on new users of angiotensin II receptor blockers or ACEIs, displayed that the administration of high cumulative ACEI doses was joined with modestly increased odds of pulmonary malignancy although the use of lower doses disclosed neutral relationships. This study contained 9652 cases of pulmonary cancer matched to 190 055 control subjects (8).

Meanwhile, Meng et al showed a total of 622 patients with pulmonary cancer in ACEIs users. They also showed female individuals displayed a significant disproportionate association, though male cases did not. Statistically significant signals of pulmonary cancer were observed in patients who were administered ACEIs, with a particularly notable association found among female patients (9).

Likewise, the study by Sipahi et al demonstrated a strong association between cumulative exposure to ARBs and an increased risk of overall malignancies, as lung cancer. They interpreted that, the risk of malignancy with ARBs (and particularly pulmonary malignancy) increases with increasing cumulative exposure to these drugs. Importantly, the strengthened risk of malignancy with long-term administration of ARB has also public health concerns (10).

A recent study conducted by Wu et al, employing a systematic review and meta-analysis, indicated that the use of ACEIs poses a higher risk for pulmonary carcinogenesis compared to the use of ARBs. This association was particularly pronounced in Asian patient populations (11).

In contrast to the above studies, Chiang et al, a retrospective investigation analyzes the risk of malignancy expansion in individuals who administered ACEIs/ ARBs for essential high blood pressure. Around, 297 688 Taiwanese patients with high blood pressure were recognized. The patients were categorized into an ACEI group, an ARB group, or a control group. This study showed regular administration of ACEIs/ARBs was not accompanying with an escalated risk of cancer expansion and was noticed to diminish overall cancer risk in this investigation (12).

Moreover, Batais et al in a meta-analysis determined that the administration of ACEIs was not connected with a strengthened risk of pulmonary malignancy. This systematic review and meta-analysis comprised thirteen observational studies involving a total of 458,686 ACEI users. The findings indicated no significant association between the administration of ACEIs and pulmonary cancer, particularly in investigations with both over five years and below five years of ACEI exposure (13).

Molecular mechanism of ACEI/ARBs on lung cancer

Angiotensin receptor blockers and ACEIs are commonly prescribed medications known for their frequent use in kidney protection. There have been some studies investigating the potential relationship between ACEIs and ARBs and the risk of lung cancer. However, recent studies have suggested that these drugs may also have potential benefits in the prevention and treatment of lung cancer (14,15).

The molecular mechanisms by which ARBs and ACEIs exert their effects on lung cancer are not fully understood, but several hypotheses have been proposed as follows:

Inhibition of the renin-angiotensin system

Both ARBs and ACEI target different components of the renin-angiotensin system pathway. ACEI inhibits the enzyme angiotensin-converting enzyme, which converts angiotensin I to angiotensin II. ARBs block the angiotensin II type 1 receptor. By inhibiting this pathway, these drugs reduce the production or effects of angiotensin II, a potent vasoconstrictor and growth factor. Angiotensin II has been shown to promote tumor growth, angiogenesis, and metastasis in various malignancies, including lung cancer. Therefore, by blocking the RAS pathway, ARBs and ACEI may inhibit these processes in lung cancer cells (16,17). Moreover, both ARBs and

ACEIs have been observed to exhibit anti-inflammatory capabilities by mitigating the production of pro-inflammatory cytokines, including interleukins and tumor necrosis factor-alpha (TNF-α). Chronic inflammation is known to play a crucial role in cancer development and progression, including lung cancer. By reducing inflammation, these drugs may help suppress tumor growth and metastasis (18,19). Moreover, apoptosis is a programmed cell death process that eliminates damaged or abnormal cells from the body. Studies have suggested that ARBs and ACEIs can induce apoptosis in lung cancer cells through various mechanisms such as activation of caspases (enzymes involved in apoptosis), inhibition of anti-apoptotic proteins, and modulation of cell survival pathways. By promoting apoptosis, these drugs may help eliminate cancer cells and inhibit tumor growth (20,21). Furthermore, angiogenesis, a pivotal process for tumor growth and metastasis, facilitates the supply of nutrients and oxygen to developing tumors. Both ARBs and ACEIs have demonstrated the ability to impede angiogenesis by diminishing the production of vascular endothelial growth factor (VEGF), a crucial protein in blood vessel formation. Through the inhibition of angiogenesis, these medications may curtail the blood supply to lung tumors, potentially suppressing their growth (22,23).

Bradykinin accumulation

ACEIs prevent the conversion of angiotensin I to angiotensin II and also reduce the degradation of bradykinin, a peptide involved in inflammation and vasodilation. Accumulation of bradykinin may lead to increased vascular permeability, inflammation, and angiogenesis, potentially promoting tumor growth. This mechanism has been suggested to play a role in the potential cancer-enhancing effects of ACE inhibitors (24,25).

Conclusion

While some studies suggest a possible enhancement effect of ACEIs on certain cancers, the current evidence is inconclusive. Clinicians should carefully weigh the potential risks and benefits of ACEI therapy in patients with a history of cancer or at high risk for developing malignancies. Further research is warranted to clarify the underlying mechanisms and establish definitive recommendations regarding the use of ACEIs in cancer patients.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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