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Lung cancer risk and the inhibitors of angiotensin converting enzyme; an updated review on recent evidence

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Abstract

The renin-angiotensin-aldosterone system (RAAS) has a significant act in the pathology of blood pressure and cancer. One of the dominant sections of angiotensin II (Ang II) and angiotensin-converting enzyme (ACE) expression generation in the human body is the capillary veins in the lung. Changes in the expression of RAAS were revealed to be included in several lung diseases. There are several studies on the anticancer effect of ACE inhibitors; however, Hicks and colleagues reported an augmented risk of 14% for advancing lung cancer for patients consuming ACE inhibitors against angiotensin receptor blockers (ARBs) administration. Several lines of evidence indicated that ARB users have a lower risk of tumor progression and metastasis and progression of lung cancer. This review has surveyed some studies about the study by Hicks et al with conflicting results. Some Hicks's study limitations are summarized here such as genetic effects, comparative study, residual confounding factors such as smoking, detection bias owing to cough, and socio-economic status. It is suggested some natural alternatives to ACE Inhibitors in here.

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Introduction

Two chief reasons for mortality worldwide are cardiovascular disease (CVD) and malignancy. Today, the trends of fatality because of CVD and malignancy are demonstrated as the reverse; deaths due to CVD have decline trend, while deaths due to cancer are staying constant or have increasing trend. One of the prevalent cardiovascular risk factors is hypertension that needs long-term treatment. Lowering blood pressure with anti-hypertensive drugs reduce deaths due to CVD while concerns increase whether the long-range application of anti-hypertensive therapy rise the risk of deaths due to malignancy (1). Additionally, hypertension has been recognized as a potential risk factor for malignancies. Possible underlying mechanisms include chronic inflammation, increased levels of vascular endothelial growth factor (VEGF; a factor that is implicated in *de novo* blood vessel formation in tumors), and impairment in arteriole walls through oxidative stress (2,3).

Renin-angiotensin-aldosterone system (RAAS) was recognized as a major regulator of blood pressure. A growing number of preclinical studies confirm the involvement of RAAS signaling and angiotensin peptides in tumor cell proliferation, growth, and progression (4,5). This evidence has prompted investigations about the effects of RAAS inhibitors for different types of cancer. Chiang et al, in a retroactive cohort study with 297 688 patients from 2000 to 2008 indicated that regular application of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is correlated with reducing overall cancer risk in the Taiwanese population. In their study, lung cancer as a study outcome was not designated and other anti-hypertensive medications are not regarded too (6). In another study, Cheung et al conducted a retrospective cohort by recruiting patients aged above 40 years who had undergone colonoscopy between 2005 and 2013 to see the effect of using

Key point

Changes in the expression of RAAS system were revealed to be included in several lung diseases. There are several studies on the anticancer effect of ACE inhibitors; however, Hicks and colleagues reported an augmented risk of 14% for advancing lung cancer for patients consuming ACE inhibitors against ARBs administration. Several lines of evidence indicated that, ARBs users have a lower risk of tumor progression and metastasis and progression of lung cancer. This review has surveyed some studies about the study by Hicks et al, with conflicting results. Some Hicks's study limitations are summarized here such as genetic effects, comparative study, residual confounding factors such as smoking, detection bias owing to cough, and socio-economic status. It is suggested some natural alternatives to ACE inhibitors in here.

ACEI/ARB on emerging colorectal cancer diagnosed at least six months after index colonoscopy. Their study has shown a negative correlation between ACEI/ARB usage and lower colorectal cancer (tumors distal to the splenic flexure). They showed every additional year of this drug's administration results in 5% reduction in adjusted hazard ratio risk (7).

A study by Catarata et al confirmed the function of the RAAS in the lung tumor and discusses whether occlusion of this pathway in clinical experiments probably works as an adjuvant therapy in lung cancer (8). While more research needs to demonstrate an association between the RAAS and lung cancers, the results propose that the RAAS is involved in the pathology of adenocarcinoma (9).

Lung cancer

Lung cancer is one of the prevalent malignancies and the leading cause of cancer deaths with the lowest survival rate compared with other frequent malignancies in the past few decades.

The ACE plays an essential function in changing angiotensin I (Ang I) to angiotensin II (Ang II). Ang II acts as multifunctional peptide that stimulates cancer cells proliferation. It modulates the growth of vascular cells during tumor angiogenesis. Studies have shown the increased Ang II production in non-small cell lung cancer tissues. Therefore, renin-angiotensin system (RAS) alterations implied by ACEI (angiotensin converting enzyme inhibitors) administration could possibly result in protective outcomes (10).

Changes in RAAS expression have been shown to occur in several lung diseases such as pulmonary fibrosis (11), pulmonary hypertension (12), and lung cancer (13). Actually, the augmented ACE expression is detected in numerous interstitial lung diseases confirms a supposed role of Ang II in lung diseases and role of ACE inhibitors (14) in attenuating them. Despite basic and pre-clinical studies regarding the effect of RAAS in cancer symbols, the available evidence concerning clinical trials particularly about lung cancer remains rare.

There is the initial report on the anticancer effect of ACE inhibitors in a retrospective cohort by Lever et al in 1998 (15). Similarly, a large, population-based cohort study by Friis et al (16), did not support a protective effect of ACE inhibitors on the development of cancer. Conversely, Bangalore et al (17) showed anti-hypertensive treatment with a combination of ACE inhibitors and ARBs increased the risk of cancer. Hicks et al reported an augmented risk for advancing lung cancer for patients consuming ACE inhibitors. This risk increased with prolonged use and was significant for more than five years. In a cohort study of approximately 1 000 000 patients who were treated between 1995 and 2015 and followed for 4.6 years, users of ACE inhibitors were 14% more likely to develop lung cancer than ARB users (18).

However, the latest meta-analysis directed by Bahaj et al was recognized only six observational studies from between 423 articles contain 634 672 ACE inhibitors users. The relative risk of lung cancer development among ACE inhibitor users was 1.02 compared to non-ACE inhibitor users. Therefore, it is concluded that no significant association exists between ACE inhibitor use and the development of lung cancer (19). The conflicting consequences are probably because of inadequate trials, the baseline bias of other comorbidities, confounding effects such as other anti-hypertensive medications, smoking habits, obesity, air pollution and other environmental exposures (20).

Several lines of evidence indicated that ARB users have a lower risk of tumor progression and metastasis (21,22) and progression of lung cancer (23-25). A retrospective observational study across the United States based on an administrative database containing 70,000 cases and above one million controls, during almost five years, ignored any link between lung cancer and ARB treatment (26). A large nationwide cohort from 1998 to 2006 by Pasternak et al concluded lack of significant relationship between the use of ARBs and increased risk of incident cancer overall or lung cancer practically (25).

A study involves 678 lung cancer patients with hypertension, 32% were in the RAS inhibitors group and the rest in the non-RAS inhibitors group. Survival was higher in RAS inhibitors and ACE inhibitors than in non-RAS inhibitors, with no statistical difference between ACE and ARB inhibitors (27).

Multivariate analysis in a retrospective review included 673 patients suffering radiotherapy for non–small-cell lung cancer (NSCLC) showed that ACE inhibitor delivery is caused a higher incidence of local failure whereas ARB had protective effects on survival (28).

It is employed nationwide population-based long study in 2020 comprised 22,384 patients in Taiwan with a design similar to that of the study by Hicks et al (18) to compare lung cancer risk in the ACE inhibitors and ARB users. They concluded that, ACE inhibitor users had a higher risk of lung cancer as a dose and time dependent response in comparison with ARB (angiotensin receptor blocker) users. In their study, air pollutants are regarded as a co-

variable for first time (29).

In a very large study over three million patients assessed lung cancer risk with ACE inhibitors and ARBs using propensity score matching from three regions of the United States. This study revealed a decreased risk of lung cancer and increased survival with ACE inhibitor administration-without dependence on subtypes of lung cancer-versus controls. This study supported the sustained use of ACE inhibitors without worry about increasing the risk of lung cancer (30).

In a study by Hsu et al, the effects of different doses of ACE and ARB inhibitors on lung cancer were compared. It has been shown that smoking is associated with a variety of lung cancers. However this association is stronger for squamous cell carcinoma. They found, the association of ACE inhibitors or ARB administration with different lung cancer types might alter because of the different lung cancer types has different survival prognosis and treatment methods (31).

Numerous studies have analyzed the association between RAS inhibitors and cancer survival and obtained inconsistent outcomes for certain types of cancers. Several studies stated that the use of RAS inhibitors was associated with improved survival in patients with NSCLC (32-34). Conversely, Aydiner et al (35) indicated lack of association between RAS inhibitors and survival in patients with NSCLC. Therefore, more trials need to evaluate the duration, interval, or type of RAS inhibitors especially ACE inhibitors and their influence on survival in patients with lung cancer.

The Hick's paper limitations

Some Hicks's study limitations include genetic effects, comparative study, residual confounding factors such as smoking, socioeconomic status, and a detection bias due to cough are existed.

Genetic effects

The pharmacokinetic research has received much attention on the ACE insertion/deletion in part due to detected difference which may be due to differences in an individual's genetics. This point should be noted that participants in the cohort study by Hicks et al were frequently Caucasian while there is significant difference for insertion/deletion in the ACE gene between Caucasian and other populations such as Asian (36).

Comparative study

The study by Hicks et al may not describe a large absolute risk and should be assessed against the improvement in morbidity and mortality obtained using ACE inhibitors against control. Further studies with long-term follow-up are essential to investigate this possible association. Hicks et al hypothesized that the protective effect of ARBs against lung cancers might be due to carcinogenic effects in ACE inhibitors. A study by Lin et al, analyzed the relationship between dosage (or duration) of ACE inhibitors using and lung cancer risk as more representative and distinctly compared ACE inhibitors users and non- ACE inhibitors users and ARB users and non-ARB users and obviously revealed the protective effects of ARBs and the deleterious effects of ACE inhibitors on lung (6).

Hicks and colleagues could not recognize the role of ACE inhibitors and ARB in lung cancer separately. In a study by Hsu et al, it is assessed the lung cancer risk of ARB and ACE inhibitors at different doses separately, in addition, lung cancers are potentially detected due to the use of ARB or ACE inhibitors (9).

Residual confounding factors

The question is whether ACE inhibitors directly caused the increase in lung cancer risk or other parameters may be involved in this association. One of the limitations of the study by Hicks et al, is excluding residual confounding factors including socioeconomic status, other medications, smoking, and a detection bias due to cough, obesity or toxic exposure when evaluating associations between anti-hypertensive drugs and cancer (37).

The poor adjustment for smoking habits

It is strongly suggested that smoking is unbalanced due to RAS homeostasis and may be responsible for the development and exacerbation of cardiovascular and pulmonary diseases, including hypertension, irregular heart regeneration, vascular dysfunction, and chronic lung disease. It is demonstrated that benefit/risk ACE inhibitors for smokers and nonsmokers are different (38,39). An important limitation of Hicks's study is that smoking and its intensity and duration is not considered.

Socioeconomic status

Prescribing models and lung cancer risk in a long-term period may be affected by socioeconomic changes. Information on socioeconomic status in the study by Hicks et al was deficient, which may vary in users of ACE inhibitors or ARB, because the marketing time for two drugs is different, ACE inhibitors presented in market in 1995 while the ARB in 2010.

Bradykinin-induced cough

ACE inhibitors induce the accumulation of bradykinin and substance P in the lungs and reduce Ang II signaling, especially when higher doses of ACE inhibitors are used (40). Accumulation of bradykinin in the lungs may sensitize the respiratory tract and increase the cough reaction. Bradykinin and substance P, which are increased during treatment with ACE inhibitors, have been shown to cause cancer migration, invasion and metastasis, and eventually cancer development. Therefore, ACEI administration is associated with a persistent cough that is demonstrated by chest imaging, however such evidence in the study by Hicks et al was not available.

The calculated risk for every 5 years of using of the ACE inhibitors is 0.2% that is a very small percentage; hence probable risk depends on the age of the patient and duration of using ACE inhibitors. It must be mentioned that the study of Hicks et al is an observational study, which has inherent limitations and a relatively low overall risk to patients, and requires in-depth study to make definitive decisions to withdraw and replacing ACE inhibitors for other classes of medications for controlling blood pressure. Stopping RAS inhibitor drugs suddenly is very dangerous, and it increases the risk of stroke or heart attack (41). Patients should talk to their healthcare providers about the risk/benefit ratio of staying on ACE inhibitors. Cough caused by ACE inhibitors has been reported to be 5% to 20%. A study by Ng et al, with 424 patients assessed the rate of withdrawal of ACE inhibitors due to cough at a primary care facility in Singapore. The incidence of withdrawal of ACE inhibitors due to cough in this study was 30.4%, which is higher than other studies (42). One selection might be to replace an ARB if there is an enduring concern. ARB acts like ACE inhibitors on a certain biological system, but at a lower level and does not increase bradykinin levels and do not develop cough. ARB does not affect enzymes such as ACE inhibitors, but recent studies have shown that ARB blocks a receptor that is stimulated by hormones and reduces the risk of lung cancer (4).

A review by Messerli et al compared the results and side effects of ACE inhibitors and ARB in patients with hypertension. ACE inhibitors are associated with cough and a very low risk of angioedema and mortality. ARBs showed equal efficacy with ACE inhibitors for blood pressure outcomes including blood pressure and different cardiovascular and renal diseases, but fewer adverse events due to withdrawal are lower with ARBs than with ACE inhibitors (43).

Additionally, the recent study by Lim et al, showed comparable outcomes for the alternative use of ARBs after initial treatment with ACE inhibitors to continued use of ACE inhibitors in patients with acute myocardial infarction suffering percutaneous coronary intervention (44).

Natural substitutes to ACE inhibitors

There are natural ACE inhibitors and substitutes to control blood pressure such as pomegranate juice, flaxseed, beet juice, apple juice, prunes, dark chocolate, kiwis, and blueberries. Foods high in flavonoids are beneficial for the heart and lowering blood pressure, such as grapes, berries, citrus fruit, beans, onions, broccoli, kale, and Brussels sprouts, as well as foods containing vitamin E, like nuts, sunflower seeds, and avocados. The Dietary Approaches to Stop Hypertension (DASH) diet and lifestyle changes such as regular exercise, weight loss, stress reduction, reduced alcohol or caffeine consumption and smoking cessation are other options to deal with high blood pressure (45,46).

Conclusion

The association of ACE inhibitors with an increased risk of lung cancer needs additional large population-based cohorts, with long-term follow-ups, to investigate the effects of RAS inhibitors on the incidence of lung cancer. Some Hicks's study limitations include genetic effects, comparative study, residual confounding factors such as smoking, socioeconomic status, and a detection bias due to cough.

Authors' contribution

MM prepared the primary draft. MK conducted the first edit. FK, NA and NK conducted the second edit. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues

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

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