



Investigating the potential association between hypertension and cancer: unveiling onco-hypertension as an innovative concept

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ABSTRACT

Hypertension and cancer show a possible association, with hypertension being a result of cancer and its treatments and also serving as a potential risk factor for the development of cancer. The term “onco-hypertension” describes the presence of hypertension in individuals who have been diagnosed with cancer. Among individuals with cancer, hypertension is the most common coexisting medical condition, occurring in 38% of cases. Cancer-related hypertension involves various mechanisms, including tumor-related factors, coexisting conditions, renal dysfunction, hormonal abnormalities, and stress-related inflammation. Cancer treatments like chemotherapy-targeted therapies and immunotherapies have the potential to influence the regulation of blood pressure through the renin-angiotensin-aldosterone system (RAAS), sodium balance, and fluid retention. Epidemiological studies suggest a potential link between hypertension and specific types of cancer, although the exact reasons and underlying mechanisms remain uncertain. Antihypertensive medications have varying associations with cancer risk. Diuretics are linked to renal cell carcinoma (RCC), thiazide medications to squamous cell carcinoma (SCC), and angiotensin-converting enzyme (ACE) inhibitors to a potential increased risk of lung cancer. However, studies on angiotensin receptor blockers (ARBs) show inconclusive results. Managing onco-hypertension may require pharmacological interventions in addition to lifestyle modifications. Antihypertensive medications commonly used include ACE inhibitors, ARBs, diuretics, calcium channel blockers, and beta-blockers. Factors such as overall health, cancer stage, concomitant medications, treatment interactions, efficacy, tolerability, and side effects guide medication selection.

Implication for health policy/practice/research/medical education:

Onco-hypertension, influenced by diverse mechanisms such as tumor-related factors and cancer treatments, presents a significant risk to blood pressure regulation. Epidemiological studies indicate links between hypertension, certain antihypertensive drugs, and cancer, emphasizing the need for a comprehensive approach to manage onco-hypertension with tailored pharmacological interventions and lifestyle adjustments. The choice of antihypertensive medications should consider individual patient characteristics, cancer stage, and potential interactions with other treatments to optimize efficacy and minimize side effects.

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Introduction

Hypertension represents a noteworthy global health concern, affecting almost 42% of adults worldwide. A variety of factors influence this condition. Recent studies have provided insights into a possible association between

hypertension and cancer. This connection may arise from the effects of cancer and its treatments, and there is also consideration of hypertension as a potential risk factor for the development of cancer (1). The term “onco-hypertension” describes the presence of hypertension

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in individuals who have been diagnosed with cancer. The prevalence of onco-hypertension varies according to the type and stage of cancer, as well as the particular treatments administered (2).

Numerous studies have reported instances of onco-hypertension across various cancer types. For example, among breast cancer patients undergoing treatment, hypertension has been observed in 25% to 71% of cases. Similarly, in renal cell carcinoma (RCC), approximately 30% to 60% of patients experience hypertension. Hypertension stands as the most prevalent coexisting medical condition, affecting 38% of cancer patients, especially those with preexisting hypertension, advanced age, and a high body mass index (3, 4).

The exact mechanisms underlying hypertension caused by cancer remain incompletely comprehended and may fluctuate based on the particular type of cancer and individual variables (5). Tumor-related factors, coexisting conditions, renal dysfunction, hormonal abnormalities, stress, and inflammation are the potential contributors to the development of hypertension in cancer patients (6).

Onco-hypertension carries implications for both the management of cancer and the overall health of patients. It can influence treatment decisions, including the choice of medications and their dosages. Moreover, if hypertension remains untreated, it can increase the risk of cardiovascular complications and negatively impact the patient's overall health (7).

Some research has suggested a correlation between hypertension and an increased risk of various cancers, such as colorectal, breast, and kidney cancer. The precise mechanisms driving this correlation are still being explored, but potential factors include chronic inflammation, oxidative stress, and abnormal angiogenesis (4,6,8). Regarding the associations between antihypertensive medications and the risk of cancer, the available evidence is inconclusive. Some studies suggest potential links between certain classes of antihypertensive drugs and cancer risk, while others show no significant correlation (1).

This review aims to summarize the existing literature on potential associations between hypertension and cancer and the optimal management strategies for onco-hypertension.

Search strategy

In this research endeavor, an extensive investigation was performed to identify relevant studies by searching multiple databases, including PubMed, EMBASE, Scopus, and DOAJ, up to October 1, 2023. To carry out the search, specific keywords including "hypertension," "cancer," "anticancer treatment," "antihypertensive drugs," and "onco-hypertension" were used. The inclusion criteria encompassed clinical trials, systematic reviews, and retrospective and prospective studies investigating the relationship between cancer and hypertension. Studies

written in languages other than English were excluded from consideration. A panel of three authors assessed the abstracts of all the studies, and the selected studies were analyzed carefully.

Potential association between hypertension and cancer *Hypertension as a consequence of cancer*

The exact pathophysiological mechanisms responsible for cancer-induced hypertension are not fully understood and may vary depending on the specific type of cancer and individual factors (6). However, several mechanisms may contribute to the development of hypertension in cancer patients. Here are some possible explanations:

Tumor-related factors: Some types of tumors can secrete substances that influence the functionality of blood vessels and contribute to the development of hypertension. For instance, in a human RCC cell line, certain vasoactive peptides, such as urotensin II, adrenomedullin, and endothelin, were found to be upregulated, potentially leading to elevated blood pressure in RCC patients. Moreover, tumors can generate elevated quantities of renin which plays a role in regulating blood pressure, or vascular endothelial growth factor (VEGF), which can induce irregular growth and constriction of blood vessels (9).

Coexisting conditions: Patients with cancer often exhibit pre-existing conditions, such as obesity, kidney disease, or cardiovascular diseases, which can predispose them to hypertension. These underlying conditions, combined with the cancer itself and its treatments, can synergistically contribute to the development of hypertension (10).

Renal dysfunction: Cancer can have a direct effect on the kidneys, which may lead to renal dysfunction. The kidneys play a crucial role in blood pressure regulation by managing fluid balance and the renin-angiotensin-aldosterone system (RAAS). Impaired kidney function can disrupt these regulations and lead to hypertension (11).

Hormonal abnormalities: some cancers, such as pheochromocytoma or adrenal cortical carcinoma, have the capacity to induce the overproduction of hormones like catecholamines or cortisol which can lead to an elevation in blood pressure (12).

Stress and inflammation: Cancer, along with the associated stress response it triggers, can increase sympathetic nervous system activity and stimulate inflammation. Both of these physiological responses have the potential to raise blood pressure (13).

Hypertension as a consequence of anticancer treatment

Various cancer treatments such as chemotherapy, targeted therapies, and immunotherapies can indeed have direct or indirect effects on blood pressure regulation. They can affect the RAAS, sodium balance, or fluid retention, which can contribute to elevated blood pressure (14).

VEGF interacts with VEGF receptor tyrosine kinases,

initiating the activation of the VEGF signaling pathway (VSP) within endothelial cells. This activation leads to the stimulation of angiogenesis, the induction of endothelial cell proliferation, and the enhancement of vessel permeability (15). VSP inhibitors, such as bevacizumab and ramucirumab, exert a direct inhibitory effect on the binding of VEGF to its specific receptors. On the other hand, the mechanism of action for sorafenib and sunitinib involves the inhibition of tyrosine kinases that become activated as a consequence of the activation of the VEGF pathway. Through their suppressive action on neovascularization, they effectively impede the progression and metastasis of tumors (15).

Up to 43% of individuals receiving VSP inhibitors experience the development of hypertension (16). A recent meta-analysis revealed that the utilization of bevacizumab is correlated with an increased risk of high-grade hypertension (17). The impact of bevacizumab on hypertension exhibits a dependency on dosage, typically commencing at a dose of 10-15 mg/kg (18). In the context of a post approval surveillance study conducted in Japan, it was observed that hypertension occurred in 13.1% of patients who were administered bevacizumab (19). Likewise, the administration of sorafenib, sunitinib, lenvatinib, and axitinib to patients diagnosed with different carcinomas has been associated with an elevated susceptibility to hypertension. The elevated blood pressure resulting from the use of these medications is corrected rapidly by discontinuation of the medications (20).

Hypertension as a potential risk factor for cancer

Epidemiological studies suggest that hypertension could potentially serve as the etiological factor for specific types of cancer. However, the exact reasons for the exclusive association between hypertension and specific cancers, as well as the underlying mechanism, remain uncertain (21). Emerging epidemiological studies have provided evidence indicating that hypertension is linked to an elevated risk of several types of cancer, including RCC, colon cancer, esophageal squamous cell carcinoma (SCC), head and neck cancers, skin SCC, postmenopausal breast cancer, and uterine adenocarcinoma (8). In a cohort study encompassing 577 799 adults, it was noted that mid-blood pressure, defined as the average of systolic and diastolic blood pressure, displayed a notable correlation with an elevated risk of total incident cancer in male individuals. On the contrary, there was no observed association in women (22). A recent meta-analysis revealed that for each 10 mm Hg elevation in both systolic and diastolic blood pressure, there was an associated increase of 10% and 22% in the risk of RCC, respectively (23).

The association between antihypertensive drugs and cancer risk

Current research has placed significant emphasis on investigating the potential risk of cancer associated with

the prolonged use of antihypertensive medications but it is important to note that these findings are based on observational studies. A systematic review comprising 27 observational studies revealed that the utilization of diuretics was correlated with a heightened risk of kidney cancer, and this risk demonstrated an upward trend with prolonged treatment duration (24). A meta-analysis, incorporating data from nine observational studies, identified a substantial correlation between the utilization of thiazide medications and an elevated risk of developing skin cancer. Specifically, the analysis highlighted a notable association between the usage of hydrochlorothiazide and the risk of SCC (25). Thiazide, a photosensitizer known for inducing DNA damage and chronic subclinical skin inflammation, is associated with an increased risk of skin cancer. However, it's unclear whether this link between thiazide use and skin cancer is independent of hypertension (26). The association between the utilization of angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors and the risk of cancer has demonstrated inconsistency across studies. This inconsistency could potentially be attributed to several factors, including inadequate control for confounding variables such as tobacco consumption and environmental exposures, restricted access to long-term datasets, and considerable diversity within the populations studied. In a cohort study conducted by Hicks et al spanning from 1995 to 2015 in the UK, the administration of ACE inhibitors was associated with a 14% higher risk of lung cancer compared to the administration of ARBs (27). However, a meta-analysis of 19 randomized controlled trials, each with a minimum follow-up duration of 12 months, revealed no statistically significant disparities in cancer risk when comparing the usage of ARBs with placebo (28).

Monitoring of onco-hypertension

Accurate measurement of blood pressure is crucial for the precise diagnosis and effective management of hypertension (29). Blood pressure measurements taken within clinical settings frequently fail to accurately represent an individual's blood pressure levels outside the clinical environment. White-coat hypertension is a commonly observed phenomenon in cancer patients undergoing psychological stress (30). Masked hypertension can also be evident in cancer patients undergoing active cancer treatment. This occurrence can be attributed to the tendency of blood pressure to rise shortly after the initiation of cancer treatment, typically within a few hours or days (20). The presence of cancer-related panic, anxiety, and pain has the potential to elevate patients' blood pressure. when measured outside of the clinical setting. Consequently, it is recommended to perform blood pressure measurements in non-clinical settings for cancer patients, especially when initiating or intensifying antihypertensive and anticancer treatments. Certain guidelines recommend using ambulatory

blood pressure monitoring as the primary approach for evaluating blood pressure in non-clinical settings. In cases where ambulatory monitoring is inaccessible or not well-tolerated, home blood pressure monitoring is suggested as a suitable alternative (31). In contrast, certain guidelines, such as those implemented in Japan, advocate for prioritizing home blood pressure measurements as the initial step when commencing and escalating antihypertensive therapy (29). A systematic review and meta-analysis of prospective studies performed by Ward et al have consistently demonstrated that blood pressure readings obtained through home monitoring devices exhibit a more strong correlation with the risk of cardiovascular disease compared to measurements taken in a clinical setting (32). However, there is a scarcity of empirical evidence about the clinical efficacy of home blood pressure monitoring specifically in the context of cancer patients.

Management of onco-hypertension

The effective management of onco-hypertension typically demands a multidisciplinary strategy that involves the collaboration of oncologists, cardiologists, and other healthcare practitioners. This collaborative effort ensures the synchronized coordination of cancer treatment and blood pressure control, considering factors such as possible drug interactions and individual patient characteristics (7). Onco-hypertension treatment involves lifestyle modifications and pharmacological interventions.

Lifestyle modifications: Non-pharmacological interventions are of utmost importance in the management of hypertension associated with cancer. Lifestyle modifications encompass various aspects, including the adoption of a nutritious diet like the Dietary Approaches to Stop Hypertension (DASH) diet, decreased consumption of sodium, consistent participation in physical exercises, maintenance of a desirable body mass, abstaining from tobacco use, and limiting alcohol intake. These lifestyle adjustments have the potential to effectively regulate blood pressure levels and enhance cardiovascular health holistically (33).

Pharmacological interventions: Pharmacological interventions may be recommended to manage and regulate blood pressure levels. Frequently utilized classes of antihypertensive medications encompass ACE inhibitors, ARBs, diuretics, calcium channel blockers (CCBs), and beta-blockers (1). The selection of medications should consider the patient's overall health, stage of cancer, other medications they may be taking, and potential interactions with cancer treatments, efficacy, tolerability, and potential side effects (34).

In certain instances, cancer treatments themselves can potentially contribute to the development of hypertension. In such scenarios, it may be cautious to assess and modify the cancer treatment regimen or explore alternative treatment options that have a reduced likelihood of

inducing hypertension (35). Dihydropyridine CCBs, such as amlodipine, may be considered the primary treatment option for patients with cancer, as amlodipine has demonstrated efficacy in reducing blood pressure levels in the majority of individuals experiencing hypertension induced by bevacizumab (36). Nevertheless, the utilization of nondihydropyridine CCBs like verapamil and diltiazem is contraindicated in patients undergoing treatment with sunitinib and sorafenib. This restriction is due to the fact that these medications function as inhibitors of the enzyme CYP3A4, potentially leading to drug interactions with sunitinib and sorafenib (37). VEGF signaling pathway inhibitors induce proteinuria, and cancer patients who have proteinuria might find potential advantages from RAAS inhibitor therapy. The utilization of RAAS inhibitors in individuals with metastatic RCC has been associated with increased overall survival compared to individuals who did not receive these medications (37). RAAS inhibitors show potential benefits for cancer patients with hypertension on VEGF inhibitors. They increase nitric oxide (NO) production, which contributes to these advantages (38). Studies on RCC patients revealed that losartan or captopril effectively reduces VEGF expression in renal tumors, leading to tumor size reduction and regression of lung metastases. This suggests that RAAS inhibitors could be a promising therapy for cancer patients with VEGF inhibitor-related hypertension (37, 39). Using long-acting nitrates or phosphodiesterase inhibitors to replace NO may also improve hypertension caused by VEGF inhibitors (37). Thiazide diuretics' blood pressure-lowering effect varies in cancer patients using VSP inhibitors (40). Caution is needed with diuretic use in patients experiencing chemotherapy-induced nausea and vomiting, as it can lead to dehydration and acute kidney injury (41). Healthcare providers should adjust antihypertensive medications if nausea and vomiting persist despite fluid replacement (42). The guidelines provided by the European Society of Cardiology/ European Society of Hypertension for managing arterial hypertension suggest the potential temporary cessation of anticancer medications in cases where blood pressure remains uncontrolled and adverse events associated with hypertension persist, despite the use of multiple antihypertensive drugs (31).

Treatment goals: The optimal blood pressure target for cancer patients may differ based on individual attributes and the presence of additional medical conditions. Generally, the objective of treatment is to attain blood pressure levels that fall within the recommended range (between 90/60 mm Hg and 120/80 mm Hg) established for the general population (6).

Conclusion

Onco-hypertension involves diverse mechanisms, including tumor-related factors, coexisting conditions, renal dysfunction, hormonal abnormalities, and stress-

related inflammation. Cancer treatments affect blood pressure regulation via the RAAS, sodium balance, and fluid retention. They pose a significant hypertension risk, particularly at specific dosages.

Epidemiological studies showed that hypertension and certain antihypertensive drugs have been linked to cancer. Managing onco-hypertension may require pharmacological interventions in addition to lifestyle modifications. Antihypertensive medications commonly used include ACE inhibitors, ARBs, diuretics, CCBs, and beta-blockers. Factors such as overall health, cancer stage, concomitant medications, treatment interactions, efficacy, tolerability, and side effects guide medication selection.

Authors' contribution

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Conflicts of interest

The authors declare no conflict of interest related to the subject matter or materials discussed in this article.

Ethical issues

The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was registered on the Research Registry website and assigned the unique identification number (UIN) reviewregistry1748, which is accessible at the following link: (<https://www.researchregistry.com/browse-the-registry#home/>). The authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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