



A narrative review on the interaction between genes and the treatment of hypertension and breast cancer

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Objective: The aim to discuss the close relationship between the common biological mechanisms of breast cancer and hypertension, inflammation and oxidative stress, breast cancer gene mutations breast cancer susceptibility gene (BRCA), G protein-coupled receptor kinase (GRK4), etc. and breast cancer treatment includes chemotherapy, Endocrine therapy, Targeted therapy and anti-angiogenesis drugs. In anti-angiogenesis drugs focusing on the mechanism of tyrosine kinase inhibitors (TKI) that may activate the rhoa/rock pathway to cause hypertension, as well as the relationship between breast cancer and antihypertensive drugs includes angiotensin-converting enzyme inhibitors (ACEIs), Calcium channel blockers (CCBs) and β -blockers (BBs) will be explored.

Background: Cardiovascular diseases (CVD) and tumors are the two major types of diseases with the highest mortality rates, while hypertension accounts for the largest proportion of CVDs. A large number of the same or similar risk factors are shared between hypertension and tumors, and they influence each other. Many patients, particularly elderly patients, often present with the coexistence of the two diseases. As medical advances have enabled clinicians to cure tumors, many patients with cancer live longer, leading to a gradual increase in the incidence of CVDs, including hypertension. With the second highest incidence among tumors, breast cancer has gradually attracted widespread attention and has been the topic of numerous studies. Studies have confirmed that CVD is one of the causes of death in elderly patients with breast cancer.

Methods: Publications from 1985 to 2020 were retrieved from the Web Of Science, Cochrane Library, PubMed, EMBASE and MEDLINE database. We used a mix of MeSH and keywords.

Conclusions: Hypertension and cancer may share a common mechanism. The screening and risk assessment of breast cancer in patients with hypertension must be strengthened. Breast cancer cardiology is the interdisciplinary study of oncology and cardiology, and in-depth research in this field may result in long-term improvements in the survival and prognosis of patients with both clinical hypertension and breast cancer.

Keywords: Hypertension; breast cancer; tumor treatment; hypertension treatment

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Introduction

Hypertension is the largest contributor to the burden of cardiovascular disease (CVD), and the prevalence of the disease is increasing in different regions (1). According to a survey, the prevalence of CVD in China is continuously increasing. The estimated number of patients with CVDs is 290 million, and the estimated number of patients with hypertension is 245 million. In other words, the incidence of hypertension accounts for 84.48% of CVD. Moreover, the control rate and treatment compliance rate of hypertension are still very low. With the continuous improvement of medical technology, the life span of patients with cancer has been extended, and millions of patients with various cancers have survived to date. However, the progress in treatment has increased the overlap between cancer and CVD, and these patients have a risk of developing CVD (2,3).

Although CVD and cancer are generally considered two separate disease entities, they share various risk factors and possible interactions (*Figure 1*). Hypertension is a CVD with a very high prevalence rate, and it is also an important cardiovascular risk factor. A study presented at the European Multidisciplinary Cancer Conference in 2011 suggested that men whose blood pressure is higher than normal have a significant increase of 10–20% in the risk of cancer, and both men and women have an increased risk of dying from cancer. In recent years, many studies have also found an association between tumors and hypertension (4,5). These diseases may be causal factors for each other, and increasing evidence confirms a close relationship between the two (*Figure 1*). Studies exploring the relationship between hypertension and tumors as well as the mechanism underlying their co-occurrence will have great benefits for clinical work.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/atm-21-2133>).

Literature search methods

Publications from 1 January 1985 to 31 December 2020 were retrieved from the Web Of Science, Cochrane Library, PubMed, EMBASE and MEDLINE databases, without any language restrictions. We used a mix of MeSH and keywords. With the following terms: Hypertension OR (Blood Pressure, High) OR (Blood Pressures, High) (High Blood Pressure) OR (High Blood Pressures) AND (Breast Neoplasm) OR (Neoplasm, Breast) OR (Breast Tumors) OR

(Breast Tumor) OR (Tumor, Breast) OR (Tumors, Breast) OR (Neoplasms, Breast) OR (Breast Cancer) OR (Cancer, Breast) OR (Mammary Cancer) OR (Cancer, Mammary) OR (Cancers, Mammary) OR (Mammary Cancers) OR (Malignant Neoplasm of Breast) OR (Breast Malignant Neoplasm) OR (Breast Malignant Neoplasms) OR (Malignant Tumor of Breast) OR (Breast Malignant Tumor) OR (Breast Malignant Tumors) OR (Cancer of Breast) OR (Cancer of the Breast) OR (Mammary Carcinoma, Human) OR (Carcinoma, Human Mammary) OR (Carcinomas, Human Mammary) OR (Human Mammary Carcinomas) OR (Mammary Carcinomas, Human) OR (Human Mammary Carcinoma) OR (Mammary Neoplasms, Human) OR (Human Mammary Neoplasm) OR (Human Mammary Neoplasms) OR (Neoplasm, Human Mammary) OR (Neoplasms, Human Mammary) OR (Mammary Neoplasm, Human) OR (Breast Carcinoma) OR (Breast Carcinomas) OR (Carcinoma, Breast) OR (Carcinomas, Breast). The final reference list was generated on the basis of relevance and originality with regard to the topics covered in this Review.

The relationship between breast cancer and hypertension (*Figure 1*)

Hypertension is a common chronic disease and a major risk factor for cardiovascular and cerebrovascular diseases and chronic kidney disease. Breast cancer is the second most common cancer in the world (1.7 million cases) and the fifth leading cause of death worldwide in 2012 (522,000 cases) (6). Arterial hypertension is closely associated with renal cell cancer development (7). Hypertension is also one of the risk factors for breast cancer, and the prevalence of hypertension and breast cancer in women increases with age (8). In particular, the risk of breast cancer is more significantly increased in postmenopausal women than in premenopausal women (9,10). Similarly, postmenopausal women with hypertension have twice the risk of breast cancer as non-hypertensive women, and postmenopausal estrogen withdrawal may be one of the causes of postmenopausal hypertension (11). One of the reasons may be the changes in estrogen levels. After menopause, the body's endocrine is prone to changes. In addition, the lower basal metabolic rate makes the body fat. The combined influence of these factors will indeed increase the prevalence of breast cancer. Other possible mechanisms require further research and exploration. The effect of postmenopausal breast cancer on CVD in elderly women is not yet clear. Compared with

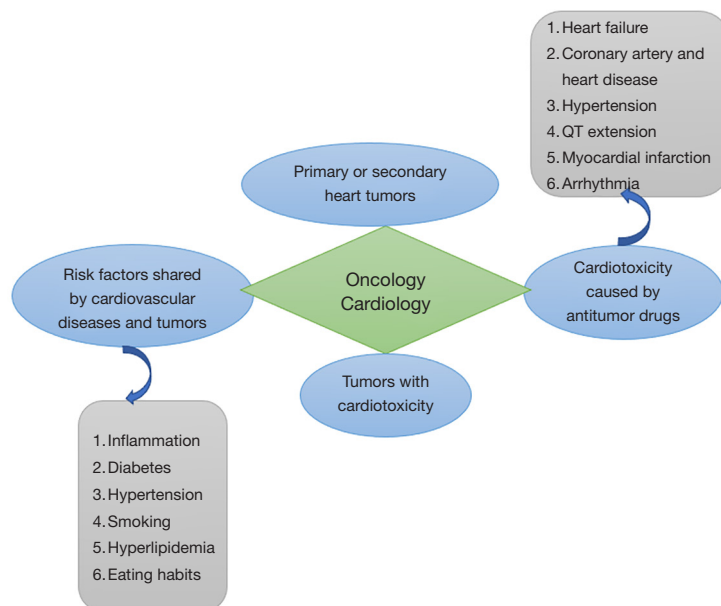


Figure 1 The subject orientation of oncology and cardiology.

elderly women without breast cancer, postmenopausal elderly women with breast cancer have a higher risk of CVD after an average of 10 years of follow-up. Only 17% of women die of breast cancer, whereas CVD is the leading cause of death (22%) (12). Therefore, among patients with breast cancer, CVD is more likely to cause death in breast cancer patients than in patients without CVD. That is, breast cancer patients with CVD risk factors have a higher mortality rate than patients without CVD.

From 1970 to 2014, the growth rate of the incidence of breast cancer among Chinese women was more than four times the growth rate in the US population (13), seriously affecting national health and social resources. A family history of breast cancer, obesity, and lack of exercise are considered risk factors for breast cancer (14,15). Similarly, obesity and a lack of exercise are also risk factors for hypertension. After controlling for obesity factors, hypertension and breast cancer are still strongly correlated. The risk of breast cancer is consistently associated with a higher BMI, and BMI is related to high blood pressure (16). In addition, the steroid hormone estradiol, which is a preventive factor for patients with hypertension, is also involved in the development of breast cancer (8). Meta-analyses showed a positive correlation between hypertension and breast cancer, but the specific mechanisms are not yet clear (9,17).

Our previous meta-analysis found a close relationship

between hypertension, antihypertensive drugs, and breast cancer (18). The incidence of hypertension in patients with breast cancer increases with age. Estrogen can delay the increase in blood pressure and participate in the development of breast cancer. The occurrence and transition of the disease is related to inflammatory mediators and angiogenesis (18).

The 2018 American Heart Association (AHA) Scientific Statement: Cardiovascular Disease and Breast Cancer stated that CVD and breast cancer have many common risk factors, such as age, diabetes, family history, drinking, hormone replacement therapy, obesity/overweight, physical activity, and smoking, amongst others. Related research shows that breast cancer treatment, particularly mediastinal and left breast cancer radiotherapy, anthracycline chemotherapy, trastuzumab, and antiangiogenic drugs, may increase the cardiovascular risk of patients with breast cancer.

The common biological mechanisms of breast cancer and hypertension involve inflammation and oxidative stress

The levels of inflammatory factors, including TNF- α , IL-6, and high sensitivity C reactive protein (hsCRP), are closely related to the occurrence and development of hypertension. Inflammatory cytokines play an important role in the development of disease in patients

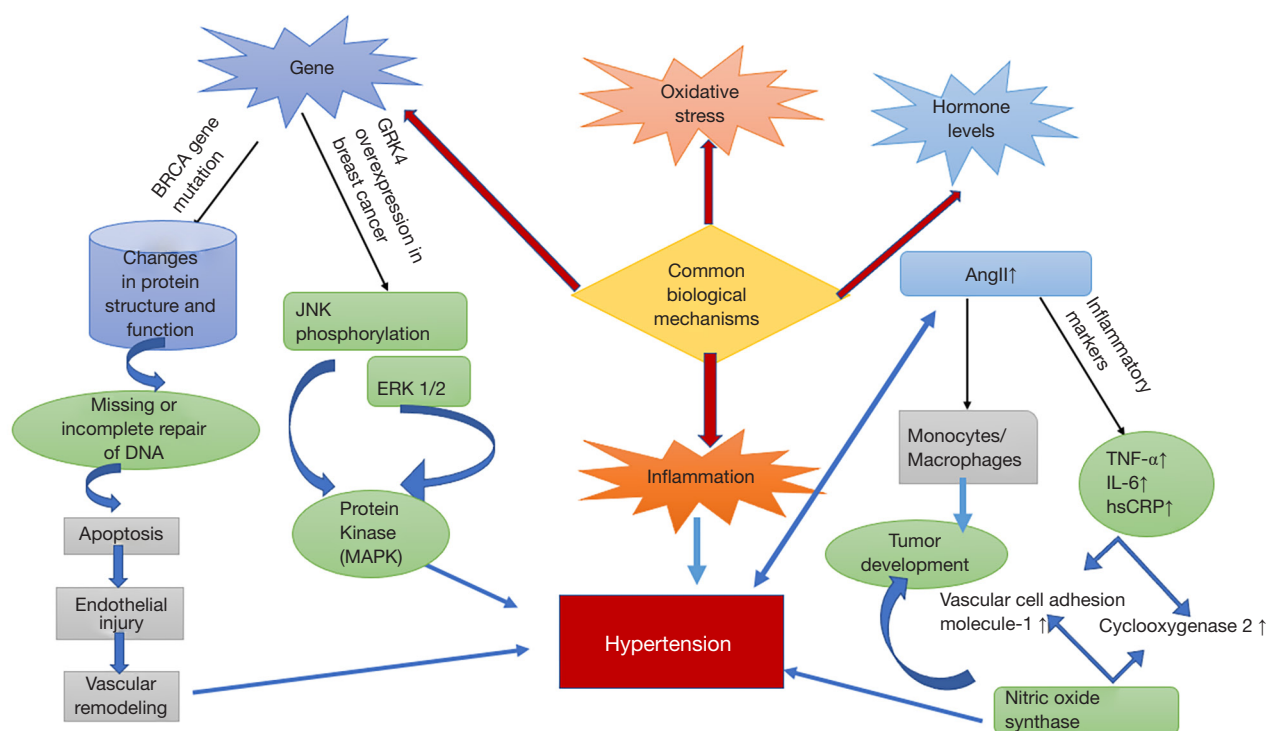


Figure 2 The common biological mechanisms of breast cancer and hypertension include chronic inflammation stimulation, oxidative stress, changes in hormone levels, and the relationship between breast cancer, hypertension and gene mutations including BRCA, and GRK4. BRCA, breast cancer susceptibility gene; GRK4, G protein-coupled receptor kinase; JNK, c-Jun N-terminal kinase; ERK1/2, extracellular regulated protein kinases 1/2; MAPK, mitogen-activated protein kinase; AngII, Angiotensin II; TNF- α , tumor necrosis factor- α ; IL-6, Interleukin-6; hsCRP, high sensitivity C reactive protein.

with hypertension, and the condition of patients with hypertension directly impacts the levels of inflammatory factors. Angiotensin II-induced hypertension increases the levels of markers of aortic monocytes/macrophages and aortic inflammation by increasing the mRNA expression of vascular cell adhesion molecule-1, cyclooxygenase 2, and inducible molecules (19) (Figure 2). The study by Zahid et al. showed that the resultant state of chronic low-grade inflammation is associated with the activation of NF- κ B signaling and elevated levels of aromatase, the rate-limiting enzyme in estrogen biosynthesis. This occurs not only in the visceral and subcutaneous fat, but also in the breast fat. The regulation of aromatase in the breast adipose stromal cell in response to inflammatory mediators is under the control of complex signaling pathways, including metabolic pathways involving LKB1/AMPK, p53, HIF1 α and PKM2 (20). The role of inflammation in promoting cancer has been confirmed (3). Inflammation in the tumor microenvironment promotes malignant transformation,

carcinogenesis, and the progression of cancer (21). On the other hand, increasing evidence shows that oxidative stress and its immediate consequences, including lipid peroxidation, are associated with multiple pathological conditions, such as atherosclerosis, cancer, and inflammation (Figure 2). Biological systems are continuously exposed to oxidants, whether they are derived from endogenous metabolic reactions or exogenous sources (such as toxins and smoking), and oxidative stress is caused by the imbalance of oxidants and antioxidants. Chronic inflammation, CVD, and common causes of cancer (such as diabetes, high blood pressure, and obesity) also cause oxidative stress (22).

Hypertension causes inflammation, and inflammation potentially promotes the occurrence and progression of breast cancer. Inflammation in the breast cancer microenvironment promotes the malignant transformation of cells and carcinogenesis, and accelerates the progression of breast cancer, forming a vicious cycle. Other factors contributing to inflammation may also include hormones,

particularly in menopausal women, who have a higher risk of breast cancer and high blood pressure, which may also be related to changes in hormone levels in the body. In addition, growth factors and cytokines are also related factors that cause hypertension and breast cancer, and a large number of experiments are currently needed to examine their roles in these diseases.

Breast cancer gene mutation and hypertension

BRCA gene mutation

The lifetime risk of breast cancer in women in Western countries is 12%, the cumulative risk of breast cancer at the age of 70 years for BRCA1 mutation carriers is 57–65%, and the corresponding cumulative risk of BRCA2 carriers is 45–49% (23,24). After excluding the death of patients with BRCA-related malignant tumors, the average life span of carriers with BRCA1/2 mutations is still reduced (25). Compared with the general population, people with mutations in the BRCA1/2 genes have a higher risk of CVD (26). The exact mechanism has not yet been elucidated, and further experiments are needed. BRCA mediates DNA damage repair and reduces the generation of reactive oxygen species (ROS). It is a protective factor for atherosclerosis. The BRCA gene plays a role in maintaining the integrity of the genome by participating in the cellular response to DNA damage. BRCA mutations lead to changes in the structure and function of the corresponding protein, causing a loss of DNA repair or incomplete repair, thereby inducing apoptosis, a process that occurs in all types of cells including vascular endothelial cells and Tumor Cell (27). This altered DNA repair of BRCA mutations may also be a cause of endothelial damage, vascular remodeling, and increased blood pressure in patients with hypertension (*Figure 2*).

The role of G protein-coupled receptor kinase (GRK4) in breast cancer and hypertension

GRKs include 7 mammalian serine/threonine protein kinases that are regulated by an oncogene called c-Myc, which is overexpressed in breast cancer and plays a role in many other cancers. The GRK4 protein is present in breast cancer cells, but not in normal breast cells. In addition, GRK4-overexpressing cells phosphorylate extracellular regulated protein kinases 1/2 (ERK 1/2) and c-Jun N-terminal kinase (JNK) to activate mitogen-activated protein kinase (MAPK) (28). Based on these results, GRK4 may be

associated with breast cancer carcinogenesis (*Figure 2*).

In addition, compared to women with normal blood pressure, women with hypertension have an approximately 15% increase in the risk of breast cancer. High levels of GRK4 have been shown to cause high blood pressure (29). A meta-analysis showed an association of the rs1801058 polymorphism in the GRK4 gene with hypertension in East Asian and European people. Among Europeans, the rs2960306 polymorphism in the GRK4 gene was also found to be significantly associated with hypertension (30). These studies further confirmed the relationship between the GRK4 gene and hypertension, but the specific mechanism remains unclear and further experiments are needed. Therefore, GRK4 may be a risk factor for hypertension and breast cancer. A drug targeting GRK4 may be used to treat patients with hypertension and breast cancer in the future.

Related mechanisms of hypertension caused by breast cancer treatment

The treatment of breast cancer is divided into local treatment and systemic treatment. Local treatment includes surgical treatment and radiotherapy, the purpose of which is to kill local tumor cells. Systemic treatment includes chemotherapy, endocrine therapy, and molecular targeted therapy. These treatments all involve the occurrence of cardiovascular events. In patients with breast cancer, cancer treatment may increase the risk of CVD through direct or indirect mechanisms. Chemotherapy, and radiotherapy directly induce structural damage to the cardiovascular system, while endocrine therapy may indirectly affect certain risk factors for CVD (31,32) (*Figure 3*).

Chemotherapy

The anthracycline cardiolipin has a higher affinity, enters mitochondria, inhibits the respiratory chain, and causes myocardial damage. Moreover, the heart lacks catalase, meaning that the antioxidant activity is weakened, and myocardial cells are rich in mitochondria, the source of ROS (*Figure 3*). Therefore, the cardiotoxicity induced by anthracycline chemotherapy includes (I) oxygen free radical damage theory, OH⁻, O₂ and anthracycline-Fe³⁺ complex; (II) calcium overload and energy metabolism theory, activate sarcoplasmic reticulum Ca²⁺ channel and inhibit Ca²⁺-ATP enzyme expression; (III) iron ion disorder theory, ferritin is reduced, active Fe²⁺ is released, participate in the reaction to produce free radicals.

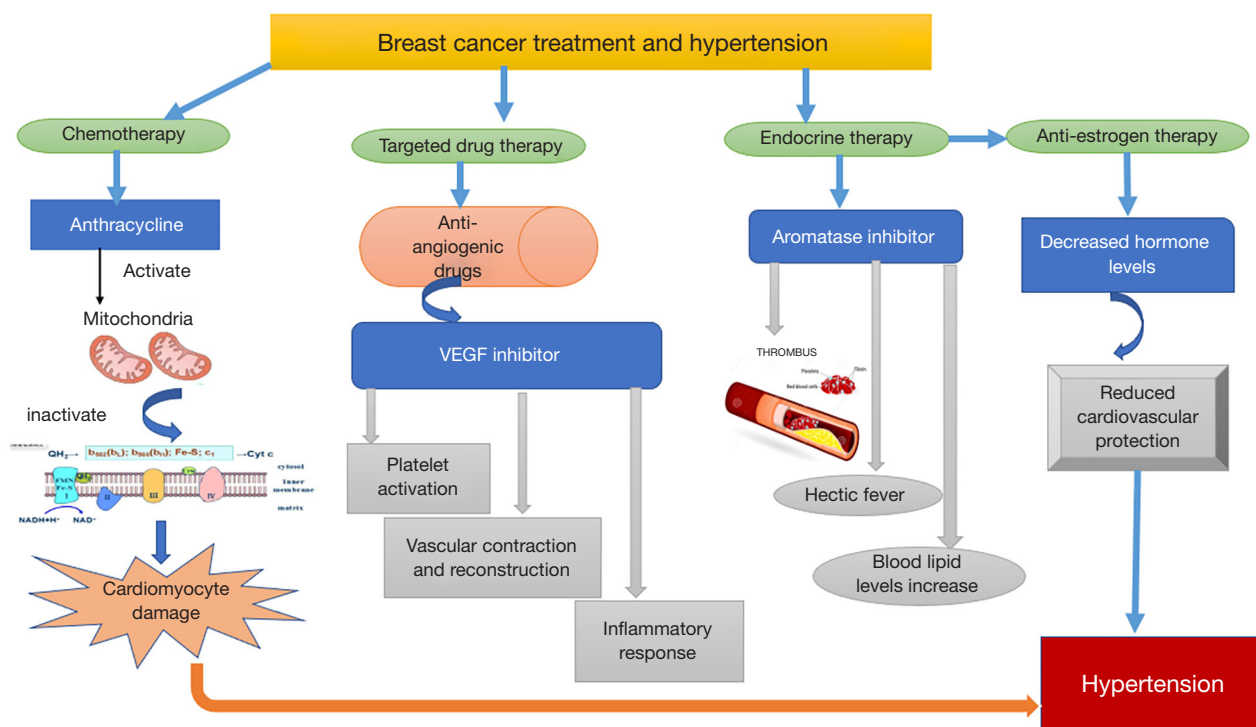


Figure 3 Related mechanisms of hypertension caused by breast cancer treatment, includes chemotherapy, endocrine therapy, and molecular targeted therapy. VEGF, Vascular endothelial growth factor.

Endocrine therapy

Patients with early breast cancer who are estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive have a better prognosis after receiving adjuvant endocrine therapy. Because more effective treatment extends the life span of these patients, they are more likely to die from CVD (including coronary heart disease and cerebrovascular disease), not breast cancer (33). Currently, the commonly used drugs for breast cancer endocrine therapy are antiestrogen drugs, aromatase inhibitors, progestins, and luteinizing hormone-releasing hormone analogs (LHRHa), amongst others (Figure 3).

Aromatase inhibitors

Aromatase inhibitors still cause adverse reactions, such as thromboembolism, hot flashes, and increased blood lipid levels, which can further increase the risk of hypertension.

Antiestrogen drugs

Tamoxifen (TAM) is currently the most commonly used antiestrogen drug. It competes with estradiol for receptors and reduces the activity of cancer cells to inhibit

their growth. Endocrine therapy is the first choice for postmenopausal patients with ER-positive breast cancer. Estrogen exerts a protective effect on cardiovascular function and can lower the blood pressure levels of female patients. Aromatase inhibitors represent an effective endocrine therapy for early and metastatic disease of hormone receptor-positive breast cancer, but by reducing the level of serum estrogen, they may also reduce the protective effect of estrogen on the cardiovascular system (34) (Figure 3). Therefore, when selecting endocrine therapy drugs for elderly patients, toxicity and side effects should be carefully evaluated as much as possible to avoid adverse effects on patients with accompanying diseases after comprehensive consideration of the patient's cardiovascular system, then a reasonable treatment plan should be developed.

Targeted therapy-related cardiovascular events

The main drugs used for breast cancer targeted drug therapy include the following categories: (I) anti-HER2 monoclonal antibodies, such as trastuzumab; (II) drugs targeting the P13K-ALK-mTOR pathway and other

pathways, such as everolimus; (III) antiangiogenesis drugs; (IV) the CD4/6 inhibitor palbociclib; (V) polyadenosine diphosphate ribose polymerase inhibitor (PARPI); and (VI) drugs targeting the PD-1 pathway and immune surveillance mechanisms. The most common side effect of antiangiogenic drugs is hypertension.

Antiangiogenic drugs

The growth of tumors depends on an adequate blood supply. As solid tumors grow, the central core becomes hypoxic, which stimulates the growth and repair pathways of physiological tissues, including the release of angiogenic growth factors to allow the formation of new blood vessels. Vascular endothelial growth factor (VEGF) plays an important role in this process, and its inhibition has become the main therapeutic target in cancer treatment (35). Hypertension caused by antiangiogenesis targeted antitumor drugs is an important direction of tumor cardiology research (36). Antiangiogenic drugs mainly refer to VEGF signaling pathway inhibitors, including VEGF-A monoclonal antibodies, VEGF inhibitors (VEGF traps), VEGF receptor monoclonal antibodies, and small molecule tyrosine kinase inhibitors (TKIs). The incidence of hypertension caused by these drugs is 11–45%, among which the incidence of severe grade 3–4 hypertension (CTCAE grade 3–4 for tumor adverse events, namely, systolic blood pressure ≥ 160 and/or diastolic blood pressure ≥ 100 mmHg, or life-threatening, requiring emergency intervention) is 2–20%. A study followed by Wildiers and others for 3 years showed that the most frequent grade 3–4 adverse events were hypertension [in 6 (15%) of 39 patients in the trastuzumab and pertuzumab group vs. 5 (12%) of 41 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group] (37). A meta-analysis showed that TKIs increase the risk of serious CVD, particularly the risk of adverse events such as thrombosis and hypertension (38). VEGF inhibitors may increase the risk of heart failure, coronary heart disease, hypertension, and thromboembolic diseases through mechanisms such as endothelial injury, vasoconstriction and remodeling, inflammation, and platelet activation (39) (*Figure 3*). Endothelin-1 (ET-1), nitric oxide (NO), and VWF are all active substances that reflect the function of the vascular endothelium and have important roles as markers of the occurrence and development of CVD and primary hypertension. When hypertension occurs, the level of NO will decrease, and ET-1 and VWF levels will increase rapidly. NO is a key factor contributing to the vascular physiological changes of smooth muscle

relaxation caused by eNOS. It plays an important role in angiogenesis. Normal endothelial cells constitutively express eNOS. When eNOS is inhibited under pathological conditions, the bioavailability of NO decreases (40).

The mechanism of hypertension caused by TKIs

TKIs are effective signal transduction inhibitors and have achieved significant progress in cancer treatment (41). By inhibiting vascular endothelial growth factor receptor (VEGFR)-mediated tumor blood vessel growth, VEGFR-TKIs have become the main treatment for many solid malignant tumors (42,43). However, the incidence of VEGFR-TKI-related cardiovascular toxicity is high and is not yet completely understood. VEGFR-TKIs can cause hypertension, left ventricular systolic dysfunction/heart failure, and atherosclerotic thrombosis, as well as prolonged QT intervals and arrhythmia (44). Hypertension is a first-order effect of VEGFR-TKI treatment and the most common manifestation of cardiovascular toxicity. Almost every trial reported a treatment-related increase in blood pressure, with up to 80% of patients experiencing hypertension, or a recurrence or worsening of the previously controlled increase in blood pressure (45). VEGFR-TKI-related hypertension may be severe and difficult to treat, but it is a dose-dependent and reversible process after stopping VEGFR-TKIs (46). However, the early identification of VEGFR-TKI-related hypertension and prompt initiation of treatment are still the main strategies.

The mechanism of hypertension during VEGFR-TKI treatment is not completely understood. Decreased bioavailability of NO is a potentially important factor in VEGFR-TKI-related hypertension. VEGF stimulates the release of NO, and VEGF inhibition is related to a reduction in NO production. EGFR-TKI treatment is also related to an increase in the level of the strong vasoconstrictor ET-1. ET-1 receptor antagonists effectively reverse acute VEGFR-TKI-related hypertension (47). According to recent studies, oxidative stress is another mechanism by which VEGFR-TKIs induce vascular dysfunction in hypertension (48). In addition, studies have confirmed that the RhoA/ROCK pathway plays an important role in the onset of salt-sensitive hypertension and the occurrence of hypertension leading to myocardial hypertrophy. The vascular contraction effect of ET-1 is enhanced by the RhoA/ROCK pathway, and ET-1 activation participates in strengthening oxidative stress, promoting peroxide production, reducing endothelial NO production, and reducing vasodilation (49).

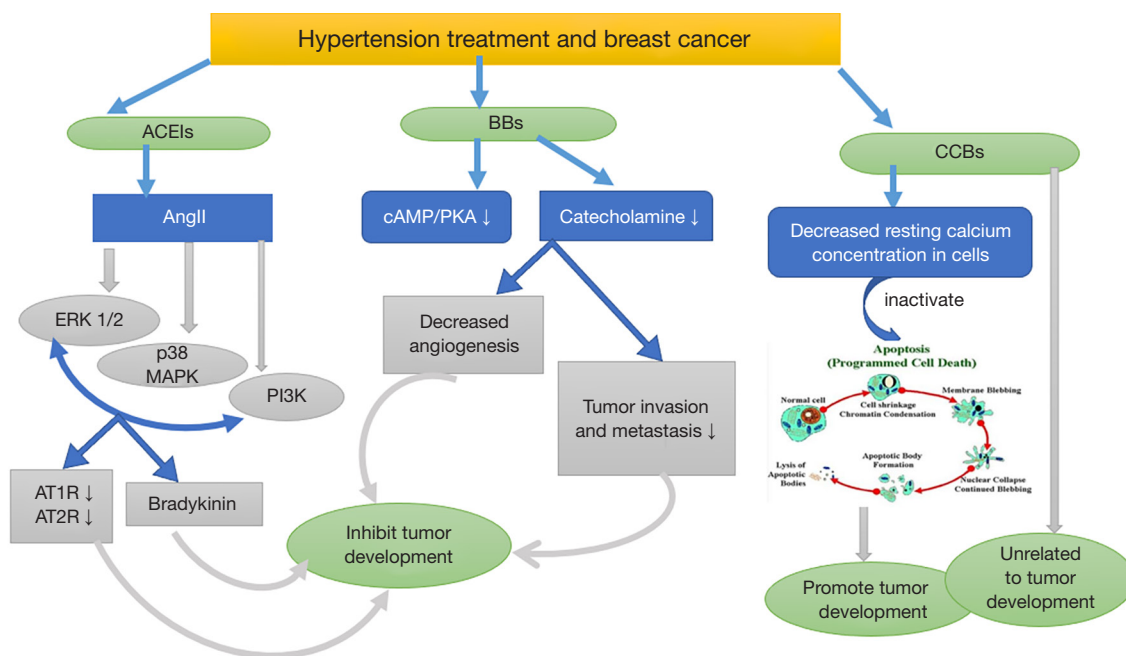


Figure 4 The relationship between antihypertensive drugs that including ACEIs, BBs, CCBs and breast cancer. ACEIs, angiotensin-converting enzyme inhibitors; BBs, β -blockers; CCBs, calcium channel blockers; cAMP, Cyclic Adenosine monophosphate; PKA, protein kinase A system; ERK1/2, extracellular regulated protein kinases 1/2; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AT1R, Angiotensin II Type 1 Receptor; AT2R, Angiotensin II Type 2 Receptor.

Therefore, the RhoA/ROCK pathway may be involved in the occurrence of hypertension caused by VEGF pathway inhibitors.

The relationship between antihypertensive drugs and breast cancer

Overall, the evidence indicates that the degree of blood pressure reduction is the main determinant of health benefits, and antihypertensive treatment has been shown to reduce the adverse effects of hypertension on CVD (50,51). In view of the wide application of antihypertensive drugs, some studies have reported a correlation between hypertension, antihypertensive drugs, and breast cancer. However, the conclusions of these studies are not consistent. A correlation between antihypertensive drugs and breast cancer has been observed in premenopausal and postmenopausal women. A large number of studies have shown that a sharp decrease in estrogen levels plays an important role in the incidence of hypertension in postmenopausal women. With the support of the ESC Practice Guidelines Committee, the 2016 ESC position paper on cancer treatment and cardiovascular

toxicity provided recommendations on the treatment of hypertension caused by tumor treatment, and angiotensin-converting enzyme inhibition was shown to improve the long-term prognosis of patients treated with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and β -blockers (BBs) (36).

ACEIs

The renin-angiotensin system (RAS) is mainly involved in regulating arterial pressure (52,53). Angiotensin II (AngII) is a bioactive peptide of the RAS, a major regulator of blood pressure and cardiovascular homeostasis, and a powerful mitogen. In addition to plasma AngII, the local RAS has been shown to function in different organs, leading to paracrine or autocrine functions of AngII. The roles of AngII in cell proliferation and migration and in some experimental models of angiogenesis suggest that this peptide may also be associated with cancer (54). AngII and advanced glycation end products (AGEs) activate ERK1/2, p38 MAPK, PI3K, and other signal transduction pathways by binding to their receptors (Figure 4). RAS includes angiotensin (AT) 2, angiotensin converting

enzyme (ACE), AT [1–7], AT receptors 1 and 2 (AT1R and AT2R), and bradykinin and its receptors. High expression of AT1Rs and AT2Rs in tumor tissues promotes tumor progression (*Figure 4*). Both ARBs and ACEIs can reverse AT2-mediated angiogenesis and mitosis in tumor tissues. ACE2 expression reduces the production of VEGF and AT1R (1). AT1R signaling activates some tyrosine kinases, including epidermal growth factor receptor (EGFR), thereby stimulating the proto-cancer pathway (55). Related research shows that AT1R is overexpressed in breast hyperplasia and ductal carcinoma (intervertebral disc) and disappears in invasive breast cancer cells (56). AT2R is expressed at low levels in normal breast ducts, but its expression is increased in breast hyperplasia, intervertebral discs, and aggressive breast cancer (57). Other data indicate that the local RAS system produces AT2, which induces the epithelial-mesenchymal transition, tumor proliferation, and angiogenesis (58,59). Therefore, the use of ACEIs in patients with breast cancer complicated by hypertension may reduce the recurrence rate of breast cancer and improve the long-term survival rate of patients with breast cancer.

Calcium channel blockers (CCBs)

CCBs are a group of antihypertensive drugs used to treat CVDs such as hypertension and angina pectoris. Although CCBs are widely used, people have long been concerned that CCBs may allow cancer cells to escape apoptosis by multiplication, leading to malignant growth (60,61). In vitro and animal models show that CCBs reduce the resting calcium concentration in cells and inhibit the expression of apoptosis-related genes (62) (*Figure 4*). Although experimental evidence has shown that CCBs may lead to the growth of malignant tumors (63,64), the study by Busby et al. of 23,669 patients with breast cancer did not find any association between drug use and breast cancer mortality. Therefore, to a certain extent, the increase in user deaths reported in previous studies may have been due to confusing instructions and other sources of bias, indicating that CCBs are safe prescriptions (65). However, the debate about the potential risks of CCBs has persisted for many years. A study of 79,453 female patients aged 55 years and older in Taiwan conducted from 2001 to 2011 showed an increased risk of breast cancer among patients using all types of antihypertensive drugs, but patients with a cumulative use of more than 6 years did not present an increased risk. Even with dihydropyridine (DHP) and CCBs, no

duration-response relationship has been found (66). Therefore, regarding its clinical significance, doctors should not sacrifice the long-term cardiovascular benefits of antihypertensive drugs simply because they are worried about the breast cancer risk that is still uncertain, and they should base their judgement on a consideration of multiple clinical factors.

BBs

Tumor proliferation is a complex multistep process, and BBs inhibit the proliferation of various breast cancer cell lines through the classical β -AR/CAMP/PKA pathway (*Figure 4*). Some epidemiological studies have shown that BBs prevent the progression of breast cancer. The mechanism may involve inhibiting the recruitment of macrophages and angiogenesis in the primary tumor, thereby affecting the progression of breast cancer (67,68). Another study described an important role for the β -AR signaling pathway in the metastasis of breast cancer. Both stress and drug stimulation of β -AR cause tumors to metastasize up to 30 times (including lymph nodes and lungs). Selective BBs inhibit this prometastatic effect by 50% to 100%. In addition, a meta-analysis showed that BBs may reduce the recurrence of breast cancer (8).

Stress associated with the neuroendocrine pathway may play a role in cancer progression (69). The stress hormone catecholamine is a potent norepinephrine receptor agonist and an inducer of cancer cell migration (70). Human breast cancer cells express β -adrenergic receptors (71). Meanwhile, catecholamine stimulation has been shown to promote angiogenesis, tumor invasion, and metastasis, and inhibits apoptosis in preclinical studies of various cancers, whereas BBs inhibit apoptosis of these cells, indicating that BBs inhibit norepinephrine-induced breast cancer metastasis (72,73) (*Figure 4*). However, meta-analyses have shown that BBs are not beneficial in reducing the total number of deaths and cancer-specific deaths or breast cancer recurrence (74). Further research is needed to assess the effects of BBs on breast cancer and its subtypes.

A meta-analysis showed that BBs reduce the risk of breast cancer recurrence, and ACEIs and CCBs are not associated with an increased breast cancer risk (8). However, the current evidence reveals a complex relationship between antihypertensive drugs and cancer-related death. In particular, controversy exists regarding the risk of breast cancer in patients with long-term use of CCBs or ACEIs. A large 12-year clinical controlled trial showed that the use of

CCBs by elderly patients with hypertension for 2–12 years was not associated with an increased risk of invasive breast cancer compared with patients who used CCBs for 1–2 years. Compared with patients taking ACEIs for 1–2 years, ACEIs exerted a protective effect on breast cancer in patients taking these drugs for 2–12 years. Specifically, the long-term use of CCBs did not increase the risk of breast cancer, and long-term use of ACEI treatment might have prevented breast cancer (75). Another report showed that CCBs inhibit the function of T cells and macrophages (76). Moreover, the immunosuppressive effect of CCBs not only affects lymphocytes in the blood but also lymphocytes in the immune microenvironment (77). Therefore, the use of CCBs is not beneficial for patients with breast cancer complicated with hypertension, which contradicts the recommendation of the guidelines, and more clinical data are needed for further verification.

Conclusions

Hypertension is one of the most important adverse reactions in the treatment of breast cancer. It restricts its drug application and may affect the prognosis of patients. However, the pathogenesis of this type of hypertension is not the same as that of essential hypertension, and the specific mechanism is still unclear. No specific prevention and treatment drugs. Apatinib is a small molecule TKI of the VEGF pathway. Exploring the pathogenesis of apatinib-induced hypertension is essential for preventing related cardiovascular events and improving the prognosis of breast cancer patients. The endothelial function damage and oxidative stress mediated by the RhoA/ROCK pathway are involved in the pathogenesis of salt-sensitive hypertension, and the two may be involved in the same pathogenesis. Therefore, we speculate that the RhoA/ROCK pathway may be involved in the occurrence of hypertension caused by apatinib, and ROCK pathway inhibitors may have therapeutic effects on it.

A certain correlation has been identified between high blood pressure and cancers in specific tissues and specific pathological forms, of which breast cancer is more closely related to hypertension. Breast cancer and hypertension are causal factors for each other and form a vicious circle. Hypertension and cancer may share a common mechanism. The screening and risk assessment of breast cancer in patients with hypertension must be strengthened, and further studies of the common mechanisms of hypertension and cancer, such as inflammation, oxidative stress, ROS,

and hormones, are needed. At the same time, severe hypertension caused by breast cancer treatment becomes an obstacle that prevents patients from continuing treatment. The biological mechanisms, molecular channels, and other factors associated with clinical treatment must be identified. Breast cancer cardiology is the interdisciplinary study of oncology and cardiology, and in-depth research in this field may result in long-term improvements in the survival and prognosis of patients with both clinical hypertension and breast cancer.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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