Use of angiotensin-converting enzyme inhibitors in gynecological cancers: Pathways and mechanisms involved (Review)

ROLAND FREDERIK LENGKEY1*, RAY SEBASTIAN SOETADJI2* and ARDO SANJAYA3,4

1Department of Obstetrics and Gynecology, Unggul Karsa Medika Hospital, Maranatha Christian University, Bandung, West Java 40218, Indonesia; 2Undergraduate Program in Medicine, Faculty of Medicine, Maranatha Christian University, Bandung, West Java 40164, Indonesia; 3Department of Anatomy, Faculty of Medicine, Maranatha Christian University, Bandung, West Java 40164, Indonesia; 4Biomedical Research Laboratory, Faculty of Medicine, Maranatha Christian University, Bandung, West Java 40164, Indonesia

Received April 3, 2024; Accepted June 18, 2024

DOI: 10.3892/wasj.2024.263

Correspondence to:
Dr Ardo Sanjaya, Department of Anatomy, Faculty of Medicine, Maranatha Christian University, Jl. Surya Sumantri No. 65, Bandung, West Java 40164, Indonesia
E-mail: Ardo.sanjaya@med.maranatha.edu

*Contributed equally

Abbreviations: ACE, angiotensin-converting enzyme; AEH, atypical endometrial hyperplasia; ARID1A, AT-rich interaction domain-containing protein 1A; ARB, angiotensin receptor blocker; CCOC, clear-cell ovarian cancer; EOC, endometrioid ovarian cancer; FAK, focal adhesion kinase; FN1, fibronectin 1; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene; MAPK, mitogen-activated protein kinase; MASr, MAS receptor; MCP, monocyte chemoattractant protein; MMR, mismatch repair system; MOC, mucinous ovarian cancer; MrGD, MAS-related G-protein coupled receptor D; OCS, ovarian carcinosarcoma; PKC, protein kinase C; PTEN, phosphatase and tensin homolog; WNT, wingless-type MMTV integration site family

Key words: angiotensin-converting enzyme inhibitors, ovarian neoplasms, cervical cancer, endometrial cancer, antitumor agent

Abstract. Gynecological cancers constitute a significant health burden for females worldwide, with cervical, endometrial and ovarian cancer being the most common types. The renin-angiotensin-aldosterone (RAA) system regulates blood pressure and is involved in various diseases, such as hypertension and heart failure. However, several studies have found that the angiotensin-I receptor (AT1R) pathway is activated in various types of cancers, including breast, pancreatic and colorectal cancers. The ATIR receptor, in particular, has been shown to induce proliferation, neovascularization and fibrosis; therefore, its activation may induce cancer progression. Several epidemiological studies have found an association between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) with reduced cancer incidence; however, others have reported unclear or even deleterious associations between ARB use and cancers. These conflicting results necessitate the further exploration of the influence of the RAA system in the development of gynecological cancers. Several new factors in the RAA system have been identified, including angiotensin-(1-7) and angiotensin-(1-9), which have been shown to play a crucial role in preventing cell proliferation and, possibly, cancer progression. The present review discusses the association between the RAA system and gynecological cancers, specifically endometrial, ovarian and cervical cancers.

Contents
1. Introduction
2. Pathogenesis and burden of gynecological cancers
3. The renin angiotensin aldosterone system pathway
4. The renin angiotensin aldosterone system pathway and cancers
5. The renin angiotensin aldosterone system pathway in gynecological cancers
6. Conclusion and future perspectives

1. Introduction

Gynecological cancers represent a significant health burden for females worldwide. The three most common types of gynecological cancer based on incidence include cervical, endometrial and ovarian cancer. Data from the Global Cancer Observatory indicate that cervical, endometrial and ovarian cancers rank as the 2nd, 6th, and 7th most common types of gynecological cancer among women, respectively (1); however, the prevalence varies significantly by geographical region and they may be caused by several factors, including obesity, availability of vaccines, number of sexual partners, and hormonal factors, such as age of menarche and oral contraceptive use (2-4).

The renin-angiotensin-aldosterone (RAA) system regulates blood pressure and is involved in several diseases, such as hypertension and heart failure. Studies have shown that this system contributes to other functions besides perfusion and blood pressure control (5). For example, the
main deleterious effects of the RAA system are mediated by the action of angiotensin-2 on angiotensin-1 receptor (AT1R). The activation of the angiotensin-2/AT1R arm, in turn, activates pathways associated with cancer, such as the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway, which results in cell proliferation and cancer cell progression (5-7). Several studies have found that the AT1R receptor pathway is activated in several types of cancer, such as breast, pancreatic and colorectal cancer (8-12). However, these findings may not be surprising considering that the AT1R receptor is involved in angiogenesis and fibrosis (13,14), which are essential cancer processes (15). Epidemiological studies have identified associations between angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) with a reduced cancer incidence (16-20). Other studies have found unclear or even inverse associations between ARB use and cancer (21-25). These findings may reflect the fact that hypertension usually occurs concurrently with diabetes and obesity, with each disease being a known risk factor for cancer development. Nevertheless, early clinical studies evaluating ARBs as an adjunct treatment for prostate cancer found beneficial effects on prostate and pancreatic cancer (26,27). Notably, the activation of other pathway arms through angiotensin derivatives, such as angiotensin-(1-7) (28) and angiotensin-(1-9) (29) play a crucial role in reducing cell proliferation and, possibly, cancer progression. Therefore, it is important to determine whether this pathway plays a role in gynecological cancers, particularly as the RAA system is a shared pathway with several common risk factors for gynecological cancers.

A common risk factor shared by gynecological cancers and the RAA system is obesity (30), which is associated with gynecological cancers due to a combination of hormonal factors, such as increased estrogen levels, and an altered tumor and immune microenvironment (30,31). Obesity may also influence cancer development through the dysregulation of the RAA system (32,33). The increased numbers of adipocytes in obese individuals cause an increase in angiotensinogen production (34,35) an essential pathology for developing obesity-induced hypertension (36,37). This dysregulation of the RAA system may lead to the development of cancer. Previous studies have found that hypertension is associated with the increased development of specific types of cancers, such as breast and endometrial cancer (38-40). These shared risk factors with gynecological cancers present an interesting pathophysiological mechanism and potential treatment strategy. A large epidemiological study of gynecological cancers revealed a protective effect of ACE inhibitors and ARBs in ovarian and cervical cancer (16); however, the same study found that the protective effects of ACE-I and ARB were associated with an increased risk of endometrial cancer (16). These conflicting findings necessitate the further exploration of the role of the RAA system in the development of gynecological cancers, particularly to determine whether RAA system blockade is effective for cancer treatment. The present review discusses the connection between the RAA system and gynecological cancers, specifically endometrial, ovarian and cervical cancers.

2. Pathogenesis and burden of gynecological cancers

Gynecological cancers constitute a significant burden among women, with the incidence of cervical and endometrial cancer reaching over one million cases worldwide and ranking as the 3rd and 4th most prevalent forms of cancer among women (1). Ovarian cancer, although much rarer, has a higher risk of mortality, particularly compared with endometrial cancer. The high prevalence of these gynecological cancers is associated with several risk factors unique to specific forms of cancers (41-43). Despite their heterogeneity, these cancers contribute to significant morbidity and a decreased quality of life; thus, they deserve further scrutiny with respect to their molecular characteristics (44).

Cervical cancers are unique among the gynecological cancers due to their association with human papillomavirus (HPV) infection (41). Perhaps the strongest evidence of their association is the geographical variations in cervical cancers that reflect a varying HPV prevalence, and reduced access to vaccines, screening and treatment. Of note, ~80% of all cervical cancers are squamous cell carcinomas, whereas the remainder are adenocarcinomas (41). Other risk factors for cervical cancer include smoking, oral contraceptive use, early sexual activity, the number of sexual partners and other infections that are transmitted sexually. HPV causes >90% of cervical cancers in women and is a central mechanism in its pathophysiology (45,46) HPV infection begins with a micro-abrasion leading to a micro-wound. The virus then infects host epithelial cells, which enables the virus to replicate. This establishes a suitable environment for neoplastic progression (46). At this stage, the immune system may eradicate the virus through the action of natural killer cells, which constitute ~85% of cases, or the virus may evade the immune system, which occurs in 15% of cases (47).

Cancer progression following HPV infection is primarily caused by the viral oncoproteins, E5, E6 and E7 (45,46). These proteins are initially responsible for suppressing the innate immune response, thus enabling the infected cells to evade the immune system. These proteins downregulate major histocompatibility complex class 1 and inhibit the function of the Toll-like receptors that produce interferon, a fundamental cytokine necessary for effective immunity against viral infections (48,49). The E6 and E7 oncoproteins further promote progression from infection to neoplasia in situ. These proteins disrupt cell cycle control typically regulated by cyclins and cyclin-dependent kinases by degrading p53 and retinoblastoma protein (pRb) (46,50,51). The disruption of p53 and pRb, two central tumor suppressor proteins, promotes cell cycle progression and bypasses the normal DNA damage checkpoints. This results in cell proliferation and the accumulation of genomic alterations that promote cancer development (46). To survive and invade distant tissues, HPV-generated tumors must acquire nutrients through the vascular network (52) Gius et al (53) reported that during the transition to a higher stage of cancer, cellular stress resulting from cell overcrowding may trigger angiogenesis and invasion through gene activation (53). Increased angiogenesis allows more nutrients to be acquired by the tumor and is beneficial for further invasion into tissues, as well as metastasis. Several genes play crucial roles in this process, including phosphatidylinositol-4,5-bisphosphate
3-kinase catalytic subalpha (PIK3CA) (46,54). HPV infection alone cannot promote cancer development. Some of these cases are HPV-negative, although HPV-positive cases are more abundant (55). Nicolás et al (56) demonstrated that HPV-negative cervical cancers have an aberrant p53 immunostaining pattern with p16 overexpression. Previous research has revealed a strong link between p53 mutation and a poor prognosis (57). Additional genetic mutations have also been identified in HPV-negative cervical cancers, such as those in the Kirsten rat sarcoma viral oncogene (KRAS), AT-rich interaction domain-containing protein 1A (ARID1A) and phosphatase and tensin homolog (PTEN) (55).

Similar to cervical cancer, endometrial cancer also has a varying incidence based on geographical distribution; however, it is not associated with a specific infection. Instead, endometrial cancers are the most common gynecological cancers in high-income countries, which have an increased prevalence of obesity and metabolic syndromes (4,58,59). Of the common types of cancer, no other type of cancer has the highest association with obesity than endometrial cancer. In fact, the association of obesity with endometrial cancer is equal to that of smoking with lung cancer, indicating that it is the most critical risk factor for endometrial cancer (60-62).

Endometrial cancers, such as the majority of cancers, have no clear pathophysiology and are caused by multiple factors. Apart from obesity, several risk factors associated with endometrial cancer include an increased age, estrogen exposure, tamoxifen use, early menarche, late menopause, low parity and genetic predisposition (59). This type of cancer is usually hormone-sensitive, reflecting the effects of excessive estrogenic stimulation caused by either obesity, exogenous hormone therapy, or prolonged estrogen stimulation caused by early menarche, late menopause and low parity. Estrogen is highly mitogenic and is involved in the physiological proliferation of the endometrium (63). However, unopposed estrogen therapy predisposes the endometrial tissue to malignant transformation, which is known as atypical endometrial hyperplasia (AEH). AEH is notorious for mutations in the PTEN gene, a known tumor suppressor gene (59). Nonetheless, the loss of tumor suppression alone is insufficient for the development of invasive carcinoma. Another common mutation involved in endometrial cancer is dysregulation of the PI3K/akt pathway, which promotes cell proliferation and possibly cancer growth (64).

Endometrial cancer pathogenesis may be divided into two types. Clinically, type 1 is known as endometrioid endometrial carcinoma, and type 2 is non-endometrioid carcinoma. Currently, >80% of the cases are diagnosed as type 1 endometrial cancer, which develops from endometrial tissue secondary to prolonged estrogen exposure. Of note, ~20% of cases are type 2 endometrial cancer developed from atrophic endometrial tissue that does not involve estrogen exposure as the main risk factor (65). Both types have different prognoses, with type 1 carcinoma clinically proven to have a better prognosis (66). Type 1 endometrial cancer accounts for 70-80% of cases with indolent clinical behavior (67). Following prolonged estrogen exposure, the endometrium may undergo hyperplasia without atypia, leading to a more advanced stage with cellular atypia, resulting in the development of endometrial carcinoma (68). Genetically, type 1 endometrial carcinoma has several gene mutations, such as the frequently encountered PTEN and KRAS mutations, as well as microsatellite instability, to the less frequently encountered p16, human epidermal growth factor receptor 2 (HER2) and E-cadherin mutations (67). Type 2 endometrial cancer has a more aggressive clinical behavior (69). It is not associated with estrogen exposure (70). Frequent genetic alterations in type 2 endometrial cancer include p53, HER2, E-cadherin, p16, KRAS, β-catenin and PTEN, with 90% of cases associated with p53 mutation (67).

Endometrial cancers may be further classified according to their molecular profiles. Based on The Cancer Genome Atlas (TCGA) data, there are four molecular subtypes of endometrial cancers (71). The high copy number group constitutes the most high-grade and aggressive type of endometrial cancer. The previously mentioned PI3K/AKT mutations are often mutated in this subgroup (59). The second tumor type is associated with microsatellite instability caused by defects in the DNA mismatch repair system (MMR). This defect results in a 10-fold greater mutational burden compared with that of the general mutational background. In addition, MMR defects are associated with Lynch syndrome, and the National Institute for Health and Care Excellence has recommended testing all endometrial cancers for this syndrome (72,73). Lynch syndrome is found in up to 3% of patients with endometrial cancers and is associated with an increased risk of future cancers (58). The third subtype contains recurrent mutations in the exonuclease domain of the polymerase-ε gene. This mutation causes up to a 100-fold greater mutational burden, but is associated with an improved prognosis. The fourth subtype is a low-copy number alteration tumor, which consists of low-grade endometrioid tumors. Although usually associated with an improved prognosis, some tumors are caused by the activation of the wingless-type MMTV integration site family (WNT)-β-catenin pathway through the mutation of catenin beta 1 (CTNNB1) and have a worse outcome (74,75). TCGA data reveal the highly heterogeneous mutation pattern associated with endometrial cancers. Further analyses of these mutations and potential treatments based on these profiles are warranted.

Ovarian cancer is a heterogeneous group of cancers with at least five known subtypes (76). This type of cancer, although rarer compared with cervical and endometrial cancers, is the most common cause of mortality from gynecological cancers (77). The primary subtype is high-grade serous ovarian carcinoma (HGSOC), which represents 70% of the cases (77). HGSOC usually presents at a late stage, with 70% of cases diagnosed at stage III (43). The recurrence of this tumor following surgery and chemotherapy is common, with a 5-year survival of ~40%. These tumors present with a complex molecular heterogeneity, copy number variations and multiple genomic variants compared with the more stable mutation patterns observed in other types of cancer (76,78). This heterogeneity is perhaps reflected in the poor improvement in the survival rates of patients with HGSOC over the past few decades (79). The whole genome sequencing of HGSOC has revealed that the majority of mutations occur in tumor suppressor genes, such as TP53, PTEN, retinoblastoma 1, neurofibromin 1 and RAD51 paralog B (80). In addition, germline mutations involving BRCA1 and BRCA2 and other
homologous recombinant repair (HRR) genes occur in approximately 50% of HGSOC cases (78). This heterogeneity makes therapy targeting specific pathways challenging, which is why platinum-based therapy continues to be the standard treatment regimen (81). However, a defect associated with the HRR genes has led to treatment with poly ADP-ribose polymerase inhibitors with notable activity as a single agent (43,77,81,82). In the future, novel methods, such as machine learning may enable the further characterization of these types of cancer (83,84).

Other ovarian cancer subtypes include endometrioid ovarian cancer (EOC), clear-cell ovarian cancer (CCOC), low-grade serous ovarian cancer (LGSOC), mucinous ovarian cancer (MOC) and ovarian carcinosarcoma (OCS) (76,77). Extensive literature covering their molecular heterogeneity can be found in the review by Hollis (78); however, several notable characteristics are discussed herein. The most common mutations for the other ovarian cancer subtypes, apart from OCS, include a typical mutation pattern also found in endometrial carcinoma. Mutations in the WNT-catenin pathway (CTNNB1), PI3K/AKT pathway (PIK3CA), ARID1A and PTEN are often found in EOC and CCOC (78). Both subtypes are also associated with MMR gene defects (Lynch syndrome). The most common mutations involve genes involved in LGSOC and MOC, such as KRAS, BRAF and NRAS, which are in the mitogen-activated protein kinase (MAPK) pathway (78,85). Other genes also play a role in MOC, such as ARID1A and PIK3CA. OCS is the least common, but the most aggressive subtype of ovarian cancer. There has been minimal molecular characterization, but TP53 mutations are present in ~90% of the cases. Although there is significant heterogeneity of the mutation patterns in ovarian cancers, two major pathways that may interact with other pathways, such as the RAA system, include the MAPK and the PI3K/AKT pathways.

3. The renin angiotensin aldosterone system pathway

The RAA system affects multiple organs and systems and is one of the most vital systems in the regulation of body homeostasis (86). Its primary function is to regulate blood pressure and consists of three main components: Renin, angiotensin-2 and aldosterone, which are interrelated (86,87).

The RAA system functions through a feedback mechanism with several stimuli affecting its activity (88). First, a decrease in renal perfusion can affect the juxtaglomerular apparatus, which secretes renin, thus activating the RAA system. Another trigger of the RAA system activity is mineral balance, such as sodium. Hyponatremia in the blood is sensed by the macula densa followed by renin secretion. The RAA system is activated in this scenario to retain sodium through an increase in sodium absorption via the renal distal convoluted tubule. The nervous system also plays a crucial role in activating the RAA system through beta 1-adrenergic receptors, which increase activity and blood pressure. Other substances also contribute through feedback mechanisms, such as potassium levels, the natriuretic peptide and angiotensinogen 1, which decrease RAA system activity (89). The main RAA system pathway begins with renin. The juxtaglomerular apparatus produces renin as its precursor, prorenin (90) which is then transformed into renin by cathepsin-B and proconvertase-1. Renin is released into the bloodstream and converts angiotensinogen, which is synthesized by the liver, to angiotensin-1 (86,87,91). However, circulating angiotensinogen-1 does not appear to have any physiological activity. Pulmonary circulation in the lungs involves an endothelial membrane containing ACE. This enzyme is primarily located in the pulmonary circulation. ACE modifies the circulating angiotensin-1, specifically at its C-terminus, into angiotensin-2, the primary effector of the RAA system. Angiotensin-2 then circulates and arrives at multiple sites throughout the body to attenuate various physiological functions (87,89).

Angiotensin-2 exerts its effects by interacting with its receptors, AT1R and angiotensin-2 type 2 receptor (AT2R). Each receptor exerts a different range of effects. AT1R is a G-protein coupled receptor distributed all over the body, but concentrated in the heart, blood vessels, kidneys, adrenal glands and the central nervous system (92). The main functions of AT1R are inducing vasoconstriction resulting from smooth muscle contraction, the release of vasopressin by the hypothalamus, and increasing sodium and water reabsorption through an increase of sodium absorption via the kidney proximal convoluted tubule. The dysregulation of this receptor is associated with several conditions, such as increased inflammation, fibrosis, oxidative stress, tissue remodeling and chronic high blood pressure that may eventually evolve into heart failure and chronic kidney disease (93,94). Another angiotensin receptor, AT2R, is also found throughout the human body. AT2R is also a G-protein coupled receptor and is abundantly expressed in the uterus, fetal tissue, heart, kidney, adrenal glands and brain. However, when coupled with angiotensin-2, AT2R produces a different effect compared with that of the AT1R receptor. AT2R induces vasodilation and natriuresis, as well as the inhibition of inflammation, fibrosis and sympathetic nerve activity (95,96).

A previous study on the RAA system revealed another active receptor known as the MAS receptor (MASr) (97). This receptor is present in several human organs, such as the brain, kidneys, adrenal glands, heart, reproductive organs and intestines. However, instead of interacting with angiotensin-2, MASr must be activated by its specific ligand, angiotensin-(1-7). Angiotensin-(1-7) is a heptapeptide produced from hydrolyzed angiotensin-1 and angiotensin-2. The production of angiotensin-(1-7) from angiotensin-1 requires an intermediate product, angiotensin-(1-9), a nonapeptide that is subsequently converted to angiotensin-(1-7) by ACE2. Angiotensin-2 can be transformed directly into angiotensin-(1-7), which is a more favorable route. In the study by Pawlik et al (98), it was demonstrated that when bound to MASr, angiotensin-(1-7) induces the production of prostaglandin E2. This generates nitric oxide and inhibits cell growth which opposes the effect of vasoconstriction and cell pro-proliferation from AT1R. Although it has its main receptor, higher levels of angiotensin-(1-7) exhibit affinity for AT1R and AT2R, whereas other researchers have shown that angiotensin-(1-7) acts competitively to inhibit AT1R (99). In the study by Xu et al (99) it was demonstrated that MASr inhibits cancer cell growth through anti-proliferative activity, the inhibition of cellular migration, invasion and epithelial-to-mesenchymal transition, and anti-angiogenic activity. Luo et al (100) demonstrated that the decreased MASr activity in breast cancer promoted cancer development. They concluded that MASr expression functions as a tumor growth inhibitor. Alamandine, which is
another novel substance in the RAA system pathway, is a peptide formed through the conversion of angiotensin-A by ACE2. It resembles angiotensin-(1-7) action, but does not bind to MASr. Instead, it acts on a different receptor, MAS-related G-protein coupled receptor D (MrgD). Research on heart disease has indicated that alamandine decreases blood pressure, cardiac remodeling, reperfusion injury and ventricular hypertrophy (87). Qaradakhi et al (101) demonstrated that alamandine exerted a similar effect as angiotensin-(1-7) by inhibiting cell proliferation, exerting anti-fibrotic effects, and vasodilatation from the alteration of prostaglandin and endogenous nitric oxide production. The study by da Silva et al (102) suggested that alamandine only affects tumor cells and reduces their mass and growth. Their experiments indicated that alamandine exerts its effect through activation of MrgD and MASr, which subsequently attenuates the PI3K/AKT/mTOR pathway (102).

These novel pathways involving alamandine and angiotensin-(1-7) represent promising targets to counteract the effects of ATIR (103). The angiotensin-2-angiotensin-(1-7)-MASr axis may be a promising therapeutic target to prevent kidney disease progression because it has a renoprotective effect on diabetic nephropathy (104). Adding the angiotensin-A-alamandine-MrgD axis to the recognition of multiple receptor-targeted therapies may lead to improvements in treatment (105). Moreover, due to its novel actions against processes, such as anti-proliferation, anti-inflammation, and reduced angiogenesis, other prevention and adjunctive strategies may be devised to overcome neoplastic disease.

4. The renin angiotensin aldosterone system pathway and cancers

The RAA system pathway exerts multiple effects exerted through its receptors, AT1R and AT2R. Docked to its different receptors, angiotensin-2 has a distinct effect on its targets. The effects of activated AT1R are more detrimental at a glance compared with AT2R. It similarly affects cancer-related processes, such as inflammation, fibrosis, oxidative stress, pro-proliferation and decreased apoptosis (93). It has been shown that AT1R is more positively associated with neoplastic disease compared with AT2R, which is frequently downregulated in specific cancers (12). Philippe (106) demonstrated that activated AT1R in endothelial cells promotes angiogenesis. Other studies have also demonstrated that AT1R activation induces the secretion of vascular endothelial growth factor (VEGF), a potent inducer of endothelial cell proliferation. Wagner et al (107) used MAP kinase kinase (MKK) and VEGF inhibitors on angiosarcoma cells, which decreased tumor activity and viability. Their findings indicate that the effect of AT1R on angiogenesis is similar to that observed in cancer cells. The review by Catarata et al (108) concluded that AT1R was overexpressed in several neoplastic tissues, including endometrial and breast cancer. Based on these findings, it can be concluded that the activation of AT1R is associated with cancer, particularly angiogenesis.

Cancer cells have the ability to metastasize. Tumor cells can migrate from the primary tumor site through the bloodstream or lymphatic vessels. The migration of cancer cells followed by the development of new vascular growth of capillaries, enables cancer cells to enter the circulation and subsequently adapt to a new environment (109). Cancer tissue must have an adequate blood supply and lymphatic tissue to survive and metastasize. Therefore, molecules such as VEGF are essential (110). Neoplastic tissue secretes various VEGF forms, such as VEGF-A, which regulates angiogenesis, tumor proliferation and metastasis, and VEGF-C and VEGF-D, which promote lymphangiogenesis, cell migration and invasion. These processes are activated through PI3K/AKT/mTOR, p38 MAPK and MKK, which are associated with AT1R activation (111). It has been shown that the overexpression of AT1R in cancer cells may activate the immunostimulatory pathway by secreting pro-inflammatory cytokines. Therefore, RAA system activation promotes neoplastic-related inflammation and the subsequent infiltration of inflammatory cells into tumor tissue (112). However, whether immune system activation during this condition is beneficial remains unclear. Angiotensin-2 interaction with ATIR on cancer cells produces pro-inflammatory cytokines, such as TGF-β, interleukin (IL)-1α, IL-1β, IL-6, IL-8, cyclooxygenase (COX)-2 and monocyte chemoattractant protein (MCP)-1 (113). These pro-inflammatory cytokines promote oxidative stress and impair myeloid and lymphoid immune cell function. In addition, some of these cytokines are also associated with increased tumor aggression, such as high levels of MCP-1 (114). In addition, COX-2 suppresses antitumor immunity and contributes to resistance to immunotherapy (115). Although at a first glance, the activation of AT1R appears to convey deleterious effects, this receptor is critical for immune cell function, such as the differentiation and maturation of macrophages (116,117). The overexpression of ACE in mice has revealed that increasing angiotensin-2 increases the pro-inflammatory and antitumor activity of macrophages compared with wild-type mice (117). Taken together, angiotensin-2 and AT1R interactions in cancer cells have complex associations, with some studies (108,111-113) supporting their role in cancer progression; however, they are also an essential component of the antitumor activity of the immune system.

The administration of ACE-I may interfere with the interaction of RAA system with cancer cells (118). Introducing ACE-I to patients with diabetic kidney disease may ameliorate the progression of angiogenesis due to a reduction in circulating levels of angiotensin-2 (5). Wang et al (119) found that the administration of ACE-I reduced neovascularization in patients with esophageal carcinoma, as evidenced by reduced CD31-positive vessel density through immunochemical staining. The review by Bryniarski et al (120) indicated that administering ACE-I decreased pro-inflammatory cytokine levels, improved immune cell function, modulated the immune response and conferred an overall protective effect against cancer. Therefore, it was hypothesized that tumor proliferation and metastasis may be reduced by decreasing the interaction of angiotensin-2 with AT1R. Therefore, lowering cytokine levels can increase angiogenesis, survival and migration, functions that are vital to cancer cells. ACE-I also shifts the conversion of angiotensin-1 to form angiotensin-(1-7), which binds to MASr (103). The increased quantity and activity of angiotensin-(1-7) and MASr has an effect similar to AT2R activity, such as decreasing angiogenesis, fibrosis, inflammation and oxidative stress (121). Taken together, the use of ACE-I may reduce cancer progression and represents a useful adjunct for cancer treatment.
5. The renin angiotensin aldosterone system pathway in gynecological cancers

ACE-I is widely used as an antihypertensive and kidney protective agent that affects the RAA system pathway. The RAA system pathway maintains homeostasis of the human body and may specifically affect certain cellular functions, such as proliferation, migration and angiogenesis (5). Thus, a strong association exists between the RAA system pathway, ACE-I and malignancy. ACE-I inhibits antiproliferative, angiogenic, pro-apoptotic, and anti-inflammatory capabilities associated with tumor cells that overexpress AT1R (122).

In ovarian cancer, some genes, such as KRAS, PTEN, PI3K and HER2, are usually mutated and promote cell overgrowth rather than death (123). A loss of PTEN activity resulting from mutated genes, and the activation of KRAS and HER2 leads to the activation of the PI3K/AKT/mTOR and ERK pathways (124-126). These pathways increase cell proliferation, survival, protein synthesis and transcription, and inhibit apoptosis via activated B-cell lymphoma-extra-large (Bcl-xL)/B-cell lymphoma-2 (Bcl-2)-associated death promoters (125). Notably, angiotensin 2 plays a crucial role in activating these pathways. Although ACE-I may not directly inhibit these pathways, it may reduce angiotensin-2 to limit its effects on cell proliferation. Nuclear factor (NF)-κB plays a critical role in ovarian cancer metastasis. A previous study found that the administration of ACE-I and AT1R blockers inhibited NF-κB (127). NF-κB activation promotes the epithelial-to-mesenchymal transition, an essential process for the migration and metastasis of cancer cells. Other mechanisms include an increase in angiogenesis and the release of matrix-degrading enzymes that promote epithelial-mesenchymal transition (128). Ovarian cancer cells express a high number of angiotensin 1 receptors. Regulska et al (129) found that at least 70% of invasive ovarian carcinoma cases had confirmed AT1R expression by immunohistochemistry. AT1R is beneficial for the growth of tumor cells. Beyazit et al (130) found that ACE levels were increased in patients with ovarian cancer. Increased serum levels of ACE concomitantly increase the levels of angiotensin-2, which exacerbates tumor growth, and suggests that ACE-I administration may benefit patients. Harding et al (131) demonstrated that women who use ACE-I have a lower mortality rate from ovarian cancer (14.8/100 person-years rate) compared with non-antihypertensive users (17.7/100 person-years rate), with an adjusted hazard ratio of 0.76.

Cervical cancer is associated with infection by the HPV. Several genes associated with the development of cervical cancer include KRAS, ARID1A, PTEN, PIK3CA, fibronectin 1 (FN1) and VEGF-A. The majority of these genes activate the PI3K pathway, which increases cellular proliferation and growth. Cervical cancer cells may proliferate abundantly in concomitant with VEGF-A expression, which accommodates cell nourishment through angiogenesis (46,54,132). The increased vascularization of cervical cancer tissue facilitates cancer cell metastasis, further promoting cancer-related mortality. Another gene usually affected by cervical cancer is the FN1 gene, which plays a role in the interaction of cells and the matrix, cellular migration, adhesion, growth and differentiation. FN1 primarily affects FAK signaling, as well as Bcl-2/Bax and N-cadherin (133). The focal adhesion kinase (FAK) signaling pathway is a nonreceptor tyrosine kinase that affects cellular adhesion, migration, proliferation, survival, and vascular permeability, which are important for cancer cell growth (134). Bcl-2/Bax and N-cadherin promote cell growth, metastasis, and anti-apoptotic activity (135). Therefore, inhibiting FN1 and the FAK signaling pathway may be beneficial to cancer patients. The mechanism associated with reduced FN1 activity remains unclear; however, PI3K and integrins may promote FN1 expression (136). Garvin et al (137) demonstrated that the administration of ACE-I reduces FN1 expression (137). FAK expression may also be inhibited by ACE-I through ACE2 activity (138,139). A decrease in FAK expression may be attributed to decreased interactions of FAK and its key activating component, the integrins, which bind with ACE2 (140). Brooks et al (141) found that lisinopril, which belongs to ACE-I, can increase ACE2 expression in tissues (141). VEGF must also be inhibited to prevent neoplastic tissue from overgrowth and metastasis. Radin et al (142) found that the inhibition of AT1R through ACE-I reduced VEGF expression and angiogenesis. This suggests that introducing ACE-I in cervical cancer may serve as an adjuvant for the primary treatment and benefit of the patients. Nguyen et al (16) reported that RAA system inhibitors, including ACE-I and ARB, are associated with a lower risk of developing cervical cancer.

Molecular components play a key role in uterine cancer in addition to estrogen exposure. Genetically, type 1 endometrial carcinoma is associated with several gene mutations, from the more frequently encountered PTEN mutations, microsatellite instability and KRAS to less frequently encountered p16, HER2 and E-cadherin (67) PTEN acts as a regulator for cell replication (143). It inhibits cell spreading and migration, focal adhesion and MAPK activation, leading to tumor cell overgrowth and angiogenesis. Therefore, the loss of PTEN is advantageous for cancer cells to grow, spread, metastasize and escape apoptosis (144). In tumors, KRAS may function as a molecular recruiter to activate proteins related to tumor growth and differentiation, and it is associated with the Raf and PI3K signaling pathways (67,145). Type 2 endometrial cancer has a more aggressive clinical behavior (69). This type of endometrial cancer is not associated with prolonged exposure to estrogen (70). Genetic alterations in type 2 endometrial cancer include p53, HER2, E-cadherin, p16, KRAS, β-catenin and PTEN. Of note, ~90% of these tumors have p53 mutations (67). HER2 is associated with the MAPK, PI3K, protein kinase C and signal transducer and activator of transcription signaling pathways, which promote cell growth and prevent apoptosis (146,147). E-cadherin is a transmembrane protein involved in cell adhesion through calcium-dependent interactions with cadherins. Mutations in E-cadherin result in decreased cell cohesion and promote cell migration, invasion and metastasis (148). The activities of several proteins, such as KRAS, PTEN, HER2 and E-cadherin may be blocked by ACE-I through inhibition of PI3K-MAPK signaling. Whether other unknown pathways are not inhibited by ACE-I, the pathways that are attenuated by ACE-I may be sufficient to prevent the growth and spread of endometrial cancer. Delforce et al (149) found that the dysregulation of the RAA system may promote tumor progression in endometrial cancer.
This suggests that ACE-I may reduce the risk of developing endometrial cancer. A summary of the interaction between the RAA system and gynecological cancers that have been discussed above is presented in Fig. 1.

6. Conclusion and future perspectives

The present review demonstrated that although gynecological cancers present with significant molecular heterogeneity, several genes are present, particularly growth regulators, such as the PI3K and MAPK pathways. The majority of these pathways interact with the RAA system through the well-known angiotensin-2/AT1R pathway, to promote cancer growth. Notably, the administration of ACE inhibitors may reduce their activation and, therefore, decrease the effects of the RAA system on cancer, a finding supported by several epidemiological studies. However, the evidence remains inconclusive and although a number of in vitro studies (7,9,10,14,100,102) have indicated that ACE administration interferes with cancer cell growth through various pathways, it is unclear which pathway dominates or influences growth. Furthermore, to date, to the best of our knowledge, no clinical trials have been performed to determine whether these effects translate into practice. In addition, in individuals without overactive RAA systems, such as those without hypertension, it is unknown whether the concomitant administration of ACE inhibitors with chemotherapy provides any benefit. Therefore, further translational studies are required. Moreover, observational studies examining whether the over-activation of the RAA system influences cancer incidence are required to determine whether this pathway significantly contributes to cancer development. Several limitations are apparent in the present review article. The present review is a narrative, and although the authors intended to be as comprehensive as possible, some articles may have been missed. In addition, the narrative may introduce bias in the interpretation of the results. Nevertheless, the present review focused on studies involving the interaction of the RAA system with cancers, potentially improving the outcomes of cancer patients. Perhaps future studies involving novel methods, such as machine learning, will unravel the complex interactions between these molecular pathways.
Acknowledgements

The authors would like to thank the Maranatha Christian University for providing the facility and database access during the preparation of the present review.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors’ contributions

RFL and RSS conceived the idea for the present review article and also wrote the initial draft of the manuscript. RSS and AS collated the evidence to be included in the present review, and AS revised and edited the manuscript. All authors contributed to the final version, and all authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References


117. Cao DY, Saito S, Veiras LC, Okwan-Duodo D, Bernstein EA, Gian JF, Bernstein KE and Khan Z: Role of angiogen-


119. Wang Q, Lei X, Zhu S and Zhang S: Angiogenisin-1 converting enzyme inhibitors suppress angiogenesis and growth of esophag-

120. Kunvariya AD, Dave SA, Modi ZJ, Patel PK and Sagar SR: Exploration of multifaceted molecular mechanism of angiogen-

121. Kunvariya AD, Dave SA, Modi ZJ, Patel PK and Sagar SR: Exploration of multifaceted molecular mechanism of angiogen-


127. Garvin AM, De Both MD, Talboom JS, Lindsey ML, Huentelman MJ and Hale TM: Transient ACE (angio-


133. Aslan O, Cremona M, Morgan C, Cheung LW, Mills GB and Hennessy BT: Preclinical evaluation and reverse phase protein Array-based profiling of PI3K and MEK inhibitors in endome-


