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

ROLAND FREDERIK LENGKEY[1*], RAY SEBASTIAN SOETADJI[2*] and ARDO SANJAYA[3,4]

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

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-1 receptor (AT1R) pathway is activated in various types of cancers, including breast, pancreatic and colorectal cancers. The AT1R 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.

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

Contents

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 subunit alpha (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. Clinicopathologically, type 1 is known as endometrioid endometrial carcinoma, and type 2 is non-endometrial 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-β 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 I, 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 resulting 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 AT1R (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 AT1R 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 increasing 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 exhibits antiproliferative, antiangiogenetic, 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.

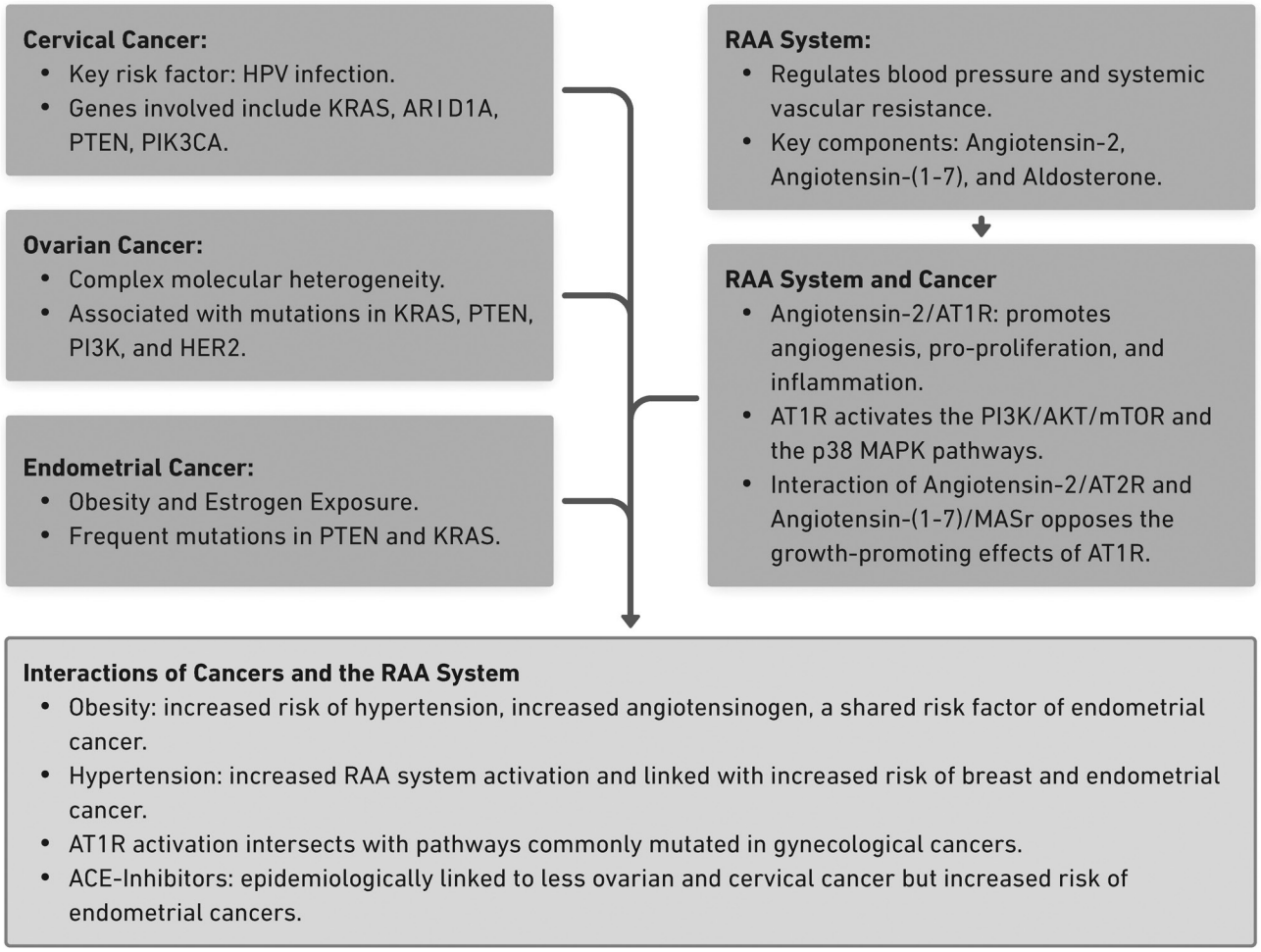

Figure 1. Summary of gynecological and RAA system interactions. The key points highlighting the interaction between cervical, ovarian and endometrial cancers and the RAA system are shown. Several overlapping pathways, such as the PI3K/AKT/mTOR, and shared risk factors, such as obesity and hypertension, are described. RAA, renin-angiotensin-aldosterone; HPV, human papillomavirus; KRAS, Kirsten rat sarcoma viral oncogene; ARID1A, AT-rich interaction domain-containing protein 1A; PTEN, phosphatase and tensin homolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PI3K, phosphoinositide 3-kinase; HER2, human epidermal growth factor receptor 2; AT1R, angiotensin-1 receptor; mTOR, mammalian target of rapamycin; MASr, MAS receptor; ACE, angiotensin-converting enzyme; AT2R, angiotensin-2 receptor.

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 overactivation 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

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Stewart SL, Lakhani N, Brown PM, Larkin OA, Moore AR and Hayes NS: Gynecologic cancer prevention and control in the national comprehensive cancer control program: Progress, current activities, and future directions. J Womens Health (Larchmt) 22: 651-657, 2013.
3. La Vecchia C: Ovarian cancer: Epidemiology and risk factors. Eur J Cancer Prev 26: 55-62, 2017.
4. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME and Singh N: Endometrial cancer. Lancet 399: 1412-1428, 2022.
5. Hassani B, Attar Z and Firouzabadi N: The renin-angiotensin-aldosterone system (RAAS) signaling pathways and cancer: Foes versus allies. Cancer Cell Int 23: 254, 2023.
6. George AJ, Thomas WG and Hannan RD: The renin-angiotensin system and cancer: Old dog, new tricks. Nat Rev Cancer 10: 745-759, 2010.
7. Zhao Y, Wang H, Li X, Cao M, Lu H, Meng Q, Pang H, Li H, Nadolny C, Dong X and Cai L: Ang II-AT1R increases cell migration through PI3K/AKT and NF-κB pathways in breast cancer. J Cell Physiol 229: 1855-1862, 2014.
8. Rasha F, Ramalingam L, Gollahon L, Rahman RL, Rahman SM, Menikdiwela K and Moustaid-Moussa N: Mechanisms linking the renin-angiotensin system, obesity, and breast cancer. Endocr Relat Cancer 26: R653-R672, 2019.
9. Coulson R, Liew SH, Connelly AA, Yee NS, Deb S, Kumar B, Vargas AC, O'Toole SA, Parslow AC, Poh A, *et al*: The angiotensin receptor blocker, Losartan, inhibits mammary tumor development and progression to invasive carcinoma. Oncotarget 8: 18640-18656, 2017.
10. Pei N, Mao Y, Wan P, Chen X, Li A, Chen H, Li J, Wan R, Zhang Y, Du H, *et al*: Angiotensin II type 2 receptor promotes apoptosis and inhibits angiogenesis in bladder cancer. J Exp Clin Cancer Res 36: 77, 2017.
11. Chen X, Meng Q, Zhao Y, Liu M, Li D, Yang Y, Sun L, Sui G, Cai L and Dong X: Angiotensin II type 1 receptor antagonists inhibit cell proliferation and angiogenesis in breast cancer. Cancer Lett 328: 318-324, 2013.
12. Almutlaq M, Alamro AA, Alamri HS, Alghamdi AA and Barhoumi T: The effect of local renin angiotensin system in the common types of cancer. Front Endocrinol (Lausanne) 12: 736361, 2021.
13. Okwan-Duodu D, Landry J, Shen XZ and Diaz R: Angiotensin-converting enzyme and the tumor microenvironment: Mechanisms beyond angiogenesis. Am J Physiol Regul Integr Comp Physiol 305: R205-R215, 2013.
14. Fan F, Tian C, Tao L, Wu H, Liu Z, Shen C, Jiang G and Lu Y: Candesartan attenuates angiogenesis in hepatocellular carcinoma via downregulating AT1R/VEGF pathway. Biomed Pharmacother 83: 704-711, 2016.
15. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discov 12: 31-46, 2022.
16. Nguyen NTH, Nguyen PA, Huang CW, Wang CH, Lin MC, Hsu MH, Bao HB, Chien SC and Yang HC: Renin-angiotensin-aldosterone system inhibitors and development of gynecologic cancers: A 23 million individual population-based study. Int J Mol Sci 24: 3814, 2023.
17. Lee SH, Park J, Park RW, Shin SJ, Kim J, Sung JD, Kim DJ and Yang K: Renin-angiotensin-aldosterone system inhibitors and risk of cancer: A population-based cohort study using a common data model. Diagnostics 12: 263, 2022.
18. Wang Z, Wei L, Yin C, Li W and Wan B: Angiotensin receptor blocker associated with a decreased risk of lung cancer: An updated meta-analysis. J Pers Med 13: 243, 2023.
19. Christian JB, Lapane KL, Hume AL, Eaton CB and Weinstock MA; VATTC Trial: Association of ACE inhibitors and angiotensin receptor blockers with keratinocyte cancer prevention in the randomized VATTC trial. J Natl Cancer Inst 100: 1223-1232, 2008.
20. Chiang YY, Chen KB, Tsai TH and Tsai WC: Lowered cancer risk with ACE inhibitors/ARBs: A population-based cohort study. J Clin Hypertens (Greenwich) 16: 27-33, 2014.
21. Yarmolinsky J, Díez-Obrero V, Richardson TG, Pigeyre M, Sjaarda J, Paré G, Walker VM, Vincent EE, Tan VY, Obón-Santacana M, *et al*: Genetically proxied therapeutic inhibition of antihypertensive drug targets and risk of common cancers: A mendelian randomization analysis. PLoS Med 19: e1003897, 2022.
22. Copland E, Canoy D, Nazarzadeh M, Bidel Z, Ramakrishnan R, Woodward M, Chalmers J, Teo KK, Pepine CJ, Davis BR, *et al*: Antihypertensive treatment and risk of cancer: An individual participant data meta-analysis. Lancet Oncol 22: 558-570, 2021.
23. Wang S, Xie L, Zhuang J, Qian Y, Zhang G, Quan X, Li L, Yu H, Zhang W, Zhao W and Qian B: Association between use of antihypertensive drugs and the risk of cancer: A population-based cohort study in Shanghai. BMC Cancer 23: 425, 2023.
24. Chen X, Yi CH and Ya KG: Renin-angiotensin system inhibitor use and colorectal cancer risk and mortality: A dose-response meta analysis. J Renin Angiotensin Aldosterone Syst 21: 1470320319895646, 2020.
25. Sipahi I: Risk of cancer with angiotensin-receptor blockers increases with increasing cumulative exposure: Meta-regression analysis of randomized trials. PLoS One 17: e0263461, 2022.
26. Murphy JE, Wo JY, Ryan DP, Clark JW, Jiang W, Yeap BY, Drapek LC, Ly L, Baglini CV, Blaszkowsky LS, *et al*: Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: A phase 2 clinical trial. JAMA Oncol 5: 1020-1027, 2019.
27. Uemura H, Hasumi H, Kawahara T, Sugiura S, Miyoshi Y, Nakaigawa N, Teranishi J, Noguchi K, Ishiguro H and Kubota Y: Pilot study of angiotensin II receptor blocker in advanced hormone-refractory prostate cancer. Int J Clin Oncol 10: 405-410, 2005.

28. Passos-Silva DG, Verano-Braga T and Santos RAS: Angiotensin-(1-7): Beyond the cardio-renal actions. Clin Sci (Lond) 124: 443-456, 2013.
29. Flores-Munoz M, Work LM, Douglas K, Denby L, Dominiczak AF, Graham D and Nicklin SA: Angiotensin-(1-9) attenuates cardiac fibrosis in the stroke-prone spontaneously hypertensive rat via the angiotensin type 2 receptor. Hypertension 59: 300-307, 2012.
30. Wichmann IA and Cuello MA: Obesity and gynecological cancers: A toxic relationship. Int J Gynaecol Obstet 155 (Suppl 1): S123-S134, 2021.
31. Liu Y, Yang J, Hilliard TS, Wang Z, Johnson J, Wang W, Harper EI, Ott C, O'Brien C, Campbell L, *et al*: Host obesity alters the ovarian tumor immune microenvironment and impacts response to standard of care chemotherapy. J Exp Clin Cancer Res 42: 165, 2023.
32. Cabandugama PK, Gardner MJ and Sowers JR: The renin angiotensin aldosterone system in obesity and hypertension: Roles in the cardiorenal metabolic syndrome. Med Clin North Am 101: 129-137, 2017.
33. Thethi T, Kamiyama M and Kobori H: The link between the renin-angiotensin-aldosterone system and renal injury in obesity and the metabolic syndrome. Curr Hypertens Rep 14: 160-169, 2012.
34. Boustany CM, Bharadwaj K, Daugherty A, Brown DR, Randall DC and Cassis LA: Activation of the systemic and adipose renin-angiotensin system in rats with diet-induced obesity and hypertension. Am J Physiol Regul Integr Comp Physiol 287: R943-R949, 2004.
35. Schütten MTJ, Houben AJHM, De Leeuw PW and Stehouwer CDA: The link between adipose tissue renin-angiotensin-aldosterone system signaling and obesity-associated hypertension. Physiology (Bethesda) 32: 197-209, 2017.
36. Yiannikouris F, Gupte M, Putnam K, Thatcher S, Charnigo R, Rateri DL, Daugherty A and Cassis LA: Adipocyte deficiency of angiotensinogen prevents obesity-induced hypertension in male mice. Hypertension 60: 1524-1530, 2012.
37. Yvan-Charvet L, Even P, Bloch-Faure M, Guerre-Millo M, Moustaid-Moussa N, Ferre P and Quignard-Boulange A: Deletion of the angiotensin type 2 receptor (AT2R) reduces adipose cell size and protects from diet-induced obesity and insulin resistance. Diabetes 54: 991-999, 2005.
38. Han H, Guo W, Shi W, Yu Y, Zhang Y, Ye X and He J: Hypertension and breast cancer risk: A systematic review and meta-analysis. Sci Rep 7: 44877, 2017.
39. Sun LM, Kuo HT, Jeng LB, Lin CL, Liang JA and Kao CH: Hypertension and subsequent genitourinary and gynecologic cancers risk: A population-based cohort study. Medicine (Baltimore) 94: e753, 2015.
40. Lindgren AM, Nissinen AM, Tuomilehto JO and Pukkala E: Cancer pattern among hypertensive patients in North Karelia, Finland. J Hum Hypertens 19: 373-379, 2005.
41. Cibula D, Raspollini MR, Planchamp F, Centeno C, Chargari C, Felix A, Fischerová D, Jahnn-Kuch D, Joly F, Kohler C, *et al*: ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer-update 2023. Int J Gynecol Cancer 33: 649-666, 2023.
42. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, Lorusso D, Marth C, Makker V, Mirza MR, *et al*: Endometrial cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 33: 860-877, 2022.
43. Colombo N, Sessa C, Du Bois A, Ledermann J, McCluggage WG, McNeish I, Morice P, Pignata S, Ray-Coquard I, Vergote I, *et al*: ESMO-ESGO consensus conference recommendations on ovarian cancer: Pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol 30: 672-705, 2019.
44. Gil-Ibanez B, Davies-Oliveira J, Lopez G, Díaz-Feijoo B, Tejerizo-Garcia A and Sehouli J: Impact of gynecological cancers on health-related quality of life: Historical context, measurement instruments, and current knowledge. Int J Gynecol Cancer 33: 1800-1806, 2023.
45. Graham SV: The human papillomavirus replication cycle, and its links to cancer progression: A comprehensive review. Clin Sci (Lond) 131: 2201-2221, 2017.
46. Balasubramaniam SD, Balakrishnan V, Oon CE and Kaur G: Key molecular events in cervical cancer development. Medicina (Kaunas) 55: 384, 2019.
47. Kurnia I, Rauf S, Hatta M, Arifuddin S, Hidayat YM, Natzir R, Kaelan C, Bukhari A, Pelupessy NU and Patelonggi IJ: Molecular Patho-mechanisms of cervical cancer (MMP1). Ann Med Surg (Lond) 77: 103415, 2022.
48. Park JS, Kim EJ, Kwon HJ, Hwang ES, Namkoong SE and Um SJ: Inactivation of interferon regulatory factor-1 tumor suppressor protein by HPV E7 oncoprotein. Implication for the E7-mediated immune evasion mechanism in cervical carcinogenesis. J Biol Chem 275: 6764-6769, 2000.
49. Ashrafi GH, Haghshenas MR, Marchetti B, O'Brien PM and Campo MS: E5 protein of human papillomavirus type 16 selectively downregulates surface HLA class I. Int J Cancer 113: 276-283, 2005.
50. Bhattacharjee R, Das SS, Biswal SS, Nath A, Das D, Basu A, Malik S, Kumar L, Kar S, Singh SK, *et al*: Mechanistic role of HPV-associated early proteins in cervical cancer: Molecular pathways and targeted therapeutic strategies. Crit Rev Oncol Hematol 174: 103675, 2022.
51. Burd EM: Human papillomavirus and cervical cancer. Clin Microbiol Rev 16: 1-17, 2003.
52. Pal A and Kundu R: Human papillomavirus E6 and E7: The cervical cancer hallmarks and targets for therapy. Front Microbiol 10: 3116, 2020.
53. Gius D, Funk MC, Chuang EY, Feng S, Huettner PC, Nguyen L, Bradbury CM, Mishra M, Gao S, Buttin BM, *et al*: Profiling microdissected epithelium and stroma to model genomic signatures for cervical carcinogenesis accommodating for covariates. Cancer Res 67: 7113-7123, 2007.
54. Vats A, Trejo-Cerro O, Thomas M and Banks L: Human papillomavirus E6 and E7: What remains? Tumour Virus Res 11: 200213, 2021.
55. Lee JE, Chung Y, Rhee S and Kim TH: Untold story of human cervical cancers: HPV-negative cervical cancer. BMB Rep 55: 429-438, 2022.
56. Nicolás I, Marimon L, Barnadas E, Saco A, Rodríguez-Carunchio L, Fusté P, Martí C, Rodriguez-Trujillo A, Torne A, Del Pino M and Ordi J: HPV-negative tumors of the uterine cervix. Mod Pathol 32: 1189-1196, 2019.
57. Zampronha Rde AC, Freitas-Junior R, Murta EFC, Michelin MA, Barbaresco AA, Adad SJ, de Oliveira AM, Rassi AB and Oton GJB: Human papillomavirus types 16 and 18 and the prognosis of patients with stage I cervical cancer. Clinics (Sao Paulo) 68: 809-814, 2013.
58. Lu KH and Broaddus RR: Endometrial cancer. N Engl J Med 383: 2053-2064, 2020.
59. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D and Oaknin A: Endometrial cancer. Nat Rev Dis Primers 7: 88, 2021.
60. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M and Renehan AG: Body mass index, hormone replacement therapy, and endometrial cancer risk: A meta-analysis. Cancer Epidemiol Biomarkers Prev 19: 3119-3130, 2010.
61. Aune D, Navarro Rosenblatt DA, Chan DSM, Vingeliene S, Abar L, Vieira AR, Greenwood DC, Bandera EV and Norat T: Anthropometric factors and endometrial cancer risk: A systematic review and dose-response meta-analysis of prospective studies. Ann Oncol 26: 1635-1648, 2015.
62. Renehan AG, Soerjomataram I, Tyson M, Egger M, Zwahlen M, Coebergh JW and Buchan I: Incident cancer burden attributable to excess body mass index in 30 European countries. Int J Cancer 126: 692-702, 2010.
63. Yu K, Huang ZY, Xu XL, Li J, Fu XW and Deng SL: Estrogen receptor function: Impact on the human endometrium. Front Endocrinol (Lausanne) 13: 827724, 2022.
64. Joshi A and Ellenson LH: PI3K/PTEN/AKT genetic mouse models of endometrial carcinoma. Adv Exp Med Biol 943: 261-273, 2017.
65. Terzic M, Aimagambetova G, Kunz J, Bapayeva G, Aitbayeva B, Terzic S and Laganà AS: Molecular basis of endometriosis and endometrial cancer: Current knowledge and future perspectives. Int J Mol Sci 22: 9274, 2021.
66. Ebring C, Marlin R, Macni J, Vallard A, Bergerac S, Beaubrun-Renard M, Joachim C and Jean-Laurent M: Type II endometrial cancer: Incidence, overall and disease-free survival in Martinique. PLoS One 18: e0278757, 2023.
67. Ohgami T and Kato K: Pathogenesis of endometrial cancer. In: Current Approaches to Endometrial Cancer. Future Medicine Ltd, Unitec House, 2 Albert Place, London N3 1QB, UK, pp18-32, 2014.
68. Miyamoto T and Shiozawa T: Two-sided role of estrogen on endometrial carcinogenesis: stimulator or suppressor? Gynecol Endocrinol 35: 370-375, 2019.
69. Lobo FD and Thomas E: Type II endometrial cancers: A case series. J Midlife Health 7: 69-72, 2016.

70. Shen F, Gao Y, Ding J and Chen Q: Is the positivity of estrogen receptor or progesterone receptor different between type 1 and type 2 endometrial cancer? Oncotarget 8: 506-511, 2017.
71. Cancer Genome Atlas Research Network: Integrated genomic analyses of ovarian carcinoma. Nature 474: 609-615, 2011.
72. Testing strategies for Lynch syndrome in people with endometrial cancer. Diagnostics guidance, 2020.
73. Stinton C, Jordan M, Fraser H, Auguste P, Court R, Al-Khudairy L, Madan J, Grammatopoulos D and Taylor-Phillips S: Testing strategies for Lynch syndrome in people with endometrial cancer: Systematic reviews and economic evaluation. Health Technol Assess 25: 1-216, 2021.
74. Liu Y, Patel L, Mills GB, Lu KH, Sood AK, Ding L, Kucherlapati R, Mardis ER, Levine DA, Shmulevich I, *et al*: Clinical significance of CTNNB1 mutation and Wnt pathway activation in endometrioid endometrial carcinoma. J Natl Cancer Inst 106: dju245, 2014.
75. Kurnit KC, Kim GN, Fellman BM, Urbauer DL, Mills GB, Zhang W and Broaddus RR: CTNNB1 (beta-catenin) mutation identifies low grade, early stage endometrial cancer patients at increased risk of recurrence. Mod Pathol 30: 1032-1041, 2017.
76. Prat J: Ovarian carcinomas: Five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch 460: 237-249, 2012.
77. Lheureux S, Gourley C, Vergote I and Oza AM: Epithelial ovarian cancer. Lancet 393: 1240-1253, 2019.
78. Hollis RL: Molecular characteristics and clinical behaviour of epithelial ovarian cancers. Cancer Lett 555: 216057, 2023.
79. Irodi A, Rye T, Herbert K, Churchman M, Bartos C, Mackean M, Nussey F, Herrington CS, Gourley C and Hollis RL: Patterns of clinicopathological features and outcome in epithelial ovarian cancer patients: 35 Years of prospectively collected data. BJOG 127: 1409-1420, 2020.
80. Patch AM, Christie EL, Etemadmoghadam D, Garsed DW, George J, Fereday S, Nones K, Cowin P, Alsop K, Bailey PJ, *et al*: Whole-genome characterization of chemoresistant ovarian cancer. Nature 521: 489-494, 2015.
81. Lheureux S, Braunstein M and Oza AM: Epithelial ovarian cancer: Evolution of management in the era of precision medicine. CA Cancer J Clin 69: 280-304, 2019.
82. Oza AM, Tinker AV, Oaknin A, Shapira-Frommer R, McNeish IA, Swisher EM, Ray-Coquard I, Bell-McGuinn K, Coleman RL, O'Malley DM, *et al*: Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2. Gynecol Oncol 147: 267-275, 2017.
83. Boehm KM, Aherne EA, Ellenson L, Nikolovski I, Alghamdi M, Vázquez-García I, Zamarin D, Long Roche K, Liu Y, Patel D, *et al*: Multimodal data integration using machine learning improves risk stratification of high-grade serous ovarian cancer. Nat Cancer 3: 723-733, 2022.
84. Li W, Liu Y, Liu W, Tang ZR, Dong S, Li W, Zhang K, Xu C, Hu Z, Wang H, *et al*: Machine learning-based prediction of lymph node metastasis among osteosarcoma patients. Front Oncol 12: 797103, 2022.
85. Bahar ME, Kim HJ and Kim DR: Targeting the RAS/RAF/MAPK pathway for cancer therapy: From mechanism to clinical studies. Signal Transduct Target Ther 8: 455, 2023.
86. Patel S, Rauf A, Khan H and Abu-Izneid T: Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother 94: 317-325, 2017.
87. Martyniak A and Tomasik PJ: A new perspective on the renin-angiotensin system. Diagnostics (Basel) 13: 16, 2022.
88. Mirabito Colafella KM, Bovée DM and Danser AHJ: The renin-angiotensin-aldosterone system and its therapeutic targets. Exp Eye Res 186: 107680, 2019.
89. Fountain JH, Kaur J and Lappin SL: Physiology, renin angiotensin system. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024.
90. Sequeira-Lopez MLS and Gomez RA: Renin cells, the kidney, and hypertension. Circ Res 128: 887-907, 2021.
91. Lu H, Cassis LA, Kooi CWV and Daugherty A: Structure and functions of angiotensinogen. Hypertens Res 39: 492-500, 2016.
92. Mascolo A, Scavone C, Rafaniello C, De Angelis A, Urbanek K, di Mauro G, Cappetta D, Berrino L, Rossi F and Capuano A: The role of renin-angiotensin-aldosterone system in the heart and lung: Focus on COVID-19. Front Pharmacol 12: 667254, 2021.
93. Kawai T, Forrester SJ, O'Brien S, Baggett A, Rizzo V and Eguchi S: AT1 receptor signaling pathways in the cardiovascular system. Pharmacol Res 125: 4-13, 2017.
94. Maranduca MA, Clim A, Pinzariu AC, Statescu C, Sascau RA, Tanase DM, Serban DN, Branisteanu DC, Branisteanu DE, Huzum B and Serban IL: Role of arterial hypertension and angiotensin II in chronic kidney disease (review). Exp Ther Med 25: 153, 2023.
95. Sun Y, Li Y, Wang M, Yue M, Bai L, Bian J, Hao W, Sun J, Zhang S and Liu H: Increased AT_2R expression is induced by AT_1R autoantibody via two axes, Klf-5/IRF-1 and circErbB4/miR-29a-5p, to promote VSMC migration. Cell Death Dis 11: 432, 2020.
96. Fatima N, Patel SN and Hussain T: Angiotensin II type 2 receptor: A target for protection against hypertension, metabolic dysfunction, and organ remodeling. Hypertension 77: 1845-1856, 2021.
97. Alenina N and dos Santos RAS: Angiotensin-(1-7) and Mas. In: The Protective Arm of the Renin Angiotensin System (RAS). Elsevier, pp155-159, 2015.
98. Pawlik MW, Kwiecien S, Ptak-Belowska A, Pajdo R, Olszanecki R, Suski M, Madej J, Targosz A, Konturek SJ, Korbut R and Brzozowski T: The renin-angiotensin system and its vasoactive metabolite angiotensin-(1-7) in the mechanism of the healing of preexisting gastric ulcers. The involvement of Mas receptors, nitric oxide, prostaglandins and proinflammatory cytokines. J Physiol Pharmacol 67: 75-91, 2016.
99. Xu J, Fan J, Wu F, Huang Q, Guo M, Lv Z, Han J, Duan L, Hu G, Chen L, *et al*: The ACE2/angiotensin-(1-7)/Mas receptor axis: Pleiotropic roles in cancer. Front Physiol 8: 276, 2017.
100. Luo Y, Tanabe E, Kitayoshi M, Nishiguchi Y, Fujiwara R, Matsushima S, Sasaki T, Sasahira T, Chihara Y, Nakae D, *et al*: Expression of MAS1 in breast cancer. Cancer Sci 106: 1240-1248, 2015.
101. Qaradakhi T, Apostolopoulos V and Zulli A: Angiotensin (1-7) and alamandine: Similarities and differences. Pharmacol Res 111: 820-826, 2016.
102. da Silva FA, Rodrigues-Ribeiro L, Melo-Braga MN, Passos-Silva DG, Sampaio WO, Gorshkov V, Kjeldsen F, Verano-Braga T and Santos RAS: Phosphoproteomic studies of alamandine signaling in CHO-MrgD and human pancreatic carcinoma cells: An antiproliferative effect is unveiled. Proteomics 22: e2100255, 2022.
103. Patel VB, Zhong J-C, Grant MB and Oudit GY: Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. Circ Res 118: 1313-1326, 2016.
104. Heyman SN, Walther T and Abassi Z: Angiotensin-(1-7)-A potential remedy for AKI: Insights derived from the COVID-19 pandemic. J Clin Med 10: 1200, 2021.
105. Hrenak J, Paulis L and Simko F: Angiotensin A/alamandine/MrgD axis: Another clue to understanding cardiovascular pathophysiology. Int J Mol Sci 17: 1098, 2016.
106. Philippe A: Unraveling the prevalence of angiotensin II type 1 receptor antibodies in hypertension. Am J Hypertens 33: 711-712, 2020.
107. Wagner MJ, Lyons YA, Siedel JH, Dood R, Nagaraja AS, Haemmerle M, Mangala LS, Chanana P, Lazar AJ, Wang WL, *et al*: Combined VEGFR and MAPK pathway inhibition in angiosarcoma. Sci Rep 11: 9362, 2021.
108. Catarata MJ, Ribeiro R, Oliveira MJ, Robalo Cordeiro C and Medeiros R: Renin-angiotensin system in lung tumor and microenvironment interactions. Cancers (Basel) 12: 1457, 2020.
109. Perea Paizal J, Au SH and Bakal C: Squeezing through the microcirculation: Survival adaptations of circulating tumour cells to seed metastasis. Br J Cancer 124: 58-65, 2021.
110. Saman H, Raza SS, Uddin S and Rasul K: Inducing angiogenesis, a key step in cancer vascularization, and treatment approaches. Cancers (Basel) 12: 1172, 2020.
111. Liu ZL, Chen HH, Zheng LL, Sun LP and Shi L: Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Signal Transduct Target Ther 8: 198, 2023.
112. Pinter M and Jain RK: Targeting the renin-angiotensin system to improve cancer treatment: Implications for immunotherapy. Sci Transl Med 9: eaan5616, 2017.
113. Brasier AR, Recinos A III and Eledrisi MS: Vascular inflammation and the renin-angiotensin system. Arterioscler Thromb Vasc Biol 22: 1257-1266, 2002.
114. Albulescu R, Codrici E, Popescu ID, Mihai S, Necula LG, Petrescu D, Teodoru M and Tanase CP: Cytokine patterns in brain tumour progression. Mediators Inflamm 2013: 979748, 2013.

115. Liu B, Qu L and Yan S: Cyclooxygenase-2 promotes tumor growth and suppresses tumor immunity. Cancer Cell Int 15: 106, 2015.
116. Zhang RM, McNerney KP, Riek AE and Bernal-Mizrachi C: Immunity and hypertension. Acta Physiol (Oxf) 231: e13487, 2021.
117. Cao DY, Saito S, Veiras LC, Okwan-Duodu D, Bernstein EA, Giani JF, Bernstein KE and Khan Z: Role of angiotensin-converting enzyme in myeloid cell immune responses. Cell Mol Biol Lett 25: 31, 2020.
118. Perini MV, Dmello RS, Nero TL and Chand AL: Evaluating the benefits of renin-angiotensin system inhibitors as cancer treatments. Pharmacol Ther 211: 107527, 2020.
119. Wang Q, Lei X, Zhu S and Zhang S: Angiotensin-I converting enzyme inhibitors suppress angiogenesis and growth of esophageal carcinoma xenografts. Dis Esophagus 25: 757-763, 2012.
120. Bryniarski P, Nazimek K and Marcinkiewicz J: Immunomodulatory activity of the most commonly used antihypertensive drugs-angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. Int J Mol Sci 23: 1772, 2022.
121. Kunvariya AD, Dave SA, Modi ZJ, Patel PK and Sagar SR: Exploration of multifaceted molecular mechanism of angiotensin-converting enzyme 2 (ACE2) in pathogenesis of various diseases. Heliyon 9: e15644, 2023.
122. Rosenthal T and Gavras I: Renin-angiotensin inhibition in combating malignancy: A review. Anticancer Res 39: 4597-4602, 2019.
123. Budiana ING, Angelina M and Pemayun TGA: Ovarian cancer: Pathogenesis and current recommendations for prophylactic surgery. J Turk Ger Gynecol Assoc 20: 47-54, 2019.
124. Martins FC, Couturier DL, Paterson A, Karnezis AN, Chow C, Nazeran TM, Odunsi A, Gentry-Maharaj A, Vrvilo A, Hein A, *et al*: Clinical and pathological associations of PTEN expression in ovarian cancer: A multicentre study from the ovarian tumour tissue analysis consortium. Br J Cancer 123: 793-802, 2020.
125. Huang L, Guo Z, Wang F and Fu L: KRAS mutation: From undruggable to druggable in cancer. Signal Transduct Target Ther 6: 386, 2021.
126. Fujimoto Y, Morita TY, Ohashi A, Haeno H, Hakozaki Y, Fujii M, Kashima Y, Kobayashi SS and Mukohara T: Combination treatment with a PI3K/Akt/mTOR pathway inhibitor overcomes resistance to anti-HER2 therapy in PIK3CA-mutant HER2-positive breast cancer cells. Sci Rep 10: 21762, 2020.
127. Harrington BS and Annunziata CM: NF-κB signaling in ovarian cancer. Cancers (Basel) 11: 1182, 2019.
128. Zhang T, Ma C, Zhang Z, Zhang H and Hu H: NF-κB signaling in inflammation and cancer. MedComm (2020) 2: 618-653, 2021.
129. Regulska K, Michalak M, Kolenda T, Kozłowska-Masłoń J, Guglas K and Stanisz B: Angiotensin-converting enzyme inhibitors for ovarian cancer? -A new adjuvant option or a silent trap. Rep Pract Oncol Radiother 28: 551-564, 2023.
130. Beyazit F, Ayhan S, Celik HT and Gungor T: Assessment of serum angiotensin-converting enzyme in patients with epithelial ovarian cancer. Arch Gynecol Obstet 292: 415-420, 2015.
131. Harding BN, Delaney JA, Urban RR and Weiss NS: Post-diagnosis use of antihypertensive medications and the risk of death from ovarian cancer. Gynecol Oncol 154: 426-431, 2019.
132. Piškur I, Topolovec Z, Bakula M, Zagorac I, Milić Vranješ I and Vidosavljević D: Expression of vascular endothelial growth factor-A (VEGF-A) in adenocarcinoma and squamous cell cervical cancer and its impact on disease progression: Single institution experience. Medicina (Lithuania) 59: 1189, 2023.
133. Zhou Y, Shu C and Huang Y: Fibronectin promotes cervical cancer tumorigenesis through activating FAK signaling pathway. J Cell Biochem 120: 10988-10997, 2019.
134. Zhou J, Yi Q and Tang L: The roles of nuclear focal adhesion kinase (FAK) on cancer: A focused review. J Exp Clin Cancer Res 38: 250, 2019.
135. Mrozik KM, Blaschuk OW, Cheong CM, Zannettino ACW and Vandyke K: N-cadherin in cancer metastasis, its emerging role in haematological malignancies and potential as a therapeutic target in cancer. BMC Cancer 18: 939, 2018.
136. Spada S, Tocci A, Di Modugno F and Nisticò P: Fibronectin as a multiregulatory molecule crucial in tumor matrisome: From structural and functional features to clinical practice in oncology. J Exp Clin Cancer Res 40: 102, 2021.
137. Garvin AM, De Both MD, Talboom JS, Lindsey ML, Huentelman MJ and Hale TM: Transient ACE (angiotensin-converting enzyme) inhibition suppresses future fibrogenic capacity and heterogeneity of cardiac fibroblast subpopulations. Hypertension 77: 904-918, 2021.
138. McLachlan CS: The angiotensin-converting enzyme 2 (ACE2) receptor in the prevention and treatment of COVID-19 are distinctly different paradigms. Clin Hypertens 26: 14, 2020.
139. Wang R, Xu J, Wu J, Gao S and Wang Z: Angiotensin-converting enzyme 2 alleviates pulmonary artery hypertension through inhibition of focal adhesion kinase expression. Exp Ther Med 22: 1165, 2021.
140. Clarke NE, Fisher MJ, Porter KE, Lambert DW and Turner AJ: Angiotensin converting enzyme (ACE) and ACE2 bind integrins and ACE2 regulates integrin signalling. PLoS One 7: e34747, 2012.
141. Brooks SD, Smith RL, Moreira AS and Ackerman HC: Oral lisinopril raises tissue levels of ACE2, the SARS-CoV-2 receptor, in healthy male and female mice. Front Pharmacol 13: 798349, 2022.
142. Radin DP, Krebs A, Maqsudlu A and Patel P: Our ACE in the HOLE: Justifying the use of angiotensin-converting enzyme inhibitors as adjuvants to standard chemotherapy. Anticancer Res 38: 45-49, 2018.
143. Stavropoulos A, Varras M, Vasilakaki T, Varra VK, Tsavari A, Varra FN, Nonni A, Kavantzas N and Lazaris AC: Expression of p53 and PTEN in human primary endometrial carcinomas: Clinicopathological and immunohistochemical analysis and study of their concomitant expression. Oncol Lett 17: 4575-4589, 2019.
144. 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 endometrial carcinoma in vitro. BMC Cancer 18: 168, 2018.
145. Manning-Geist BL, Liu YL, Devereaux KA, Paula ADC, Zhou QC, Ma W, Selenica P, Ceyhan-Birsoy O, Moukarzel LA, Hoang T, *et al*: Microsatellite instability-high endometrial cancers with MLH1 promoter hypermethylation have distinct molecular and clinical profiles. Clin Cancer Res 28: 4302-4311, 2022.
146. Erickson BK, Najjar O, Damast S, Blakaj A, Tymon-Rosario J, Shahi M, Santin A, Klein M, Dolan M, Cimino-Mathews A, *et al*: Human epidermal growth factor 2 (HER2) in early stage uterine serous carcinoma: A multi-institutional cohort study. Gynecol Oncol 159: 17-22, 2020.
147. Elnashar AT, Hassab Elnaby NED, Abdellatef AA and Salem MN: Her-2 neu expression in endometrial carcinoma. Med J Cairo Univ 86: 69-76, 2018.
148. Florescu MM, Pirici D, Simionescu CE, Stepan AE, Mărgăritescu C, Tudorache Ş and Ciurea RN: E-cadherin and β-catenin immunoexpression in endometrioid endometrial carcinoma. Rom J Morphol Embryol 57: 1235-1240, 2016.
149. Delforce SJ, Lumbers ER, Corbisier de Meaultsart C, Wang Y, Proietto A, Otton G, Scurry J, Verrills NM, Scott RJ and Pringle KG: Expression of renin-angiotensin system (RAS) components in endometrial cancer. Endocr Connect 6: 9-19, 2017.