REVIEW

Utility of Matrix Metalloproteinases in the Diagnosis, Monitoring and Prognosis of Ovarian Cancer Patients

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Abstract: Ovarian cancer is one of the most common gynecologic malignancies. It is characterized by a high mortality rate, which is mainly due to the asymptomatic course of the disease. In light of the high mortality rate and increasing morbidity, new diagnostic methods are being explored to enable earlier detection, better monitoring, and improved prognosis. Such diagnostic methods include the assessment of tumor markers in various biological samples. Among the markers currently being investigated, extracellular matrix metalloproteinases (MMPs) are of particular interest. The objective of this article was to compile the existing knowledge of MMPs in ovarian cancer patients and to describe their potential diagnostic utility. Additionally, this article provides an overview of the symptoms, complications, and risk factors associated with ovarian cancer and the role of MMPs in physiology and pathology. Preliminary results indicate that tissue expression and blood and body fluid levels of MMPs may be different in ovarian cancer patients than in healthy women. The expression and concentration of individual MMPs have been shown to be correlated with cancer stage and disease severity. In addition, the preliminary value of some of these enzymes in predicting prognosis is discussed. However, as the amount of data is limited, more studies are needed to fully evaluate the potential function of individual MMPs in ovarian cancer patients. Based on the knowledge gathered for this article, it seems that MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, are tentatively the most useful. A thorough evaluation of their utility as modern biomarkers in ovarian cancer requires further investigation.

Keywords: carcinogenesis, extracellular matrix metalloproteinases, ovarian cancer, tumor markers

Introduction

The number of women developing gynecologic cancers, including ovarian cancer, is steadily increasing. In 90% of cases, ovarian cancer originates from epithelial cells; ovarian cancers of epithelial origin are referred to as ovarian carcinomas or ovarian epithelial.[1–3] Ovarian cancer is one of the most common gynecologic malignancies, ranking third in incidence after cervical and endometrial cancers, accounting for 3.4% of all cancers types diagnosed in women. Ovarian cancer has a poor prognosis and the highest mortality rate of all gynecologic cancers. According to World Health Organization reports, less than 30% of patients survive more than five years after diagnosis. This unfavorable prognosis results not only from a lack of effective screening tests but also from the usually asymptomatic or minimally symptomatic disease progression—most patients are diagnosed at an advanced stage, and 60% have metastatic foci at the time of diagnosis.[2–5]

Considering the high mortality rate, asymptomatic course, lack of effective screening tests, and increasing number of diagnosed cases, novel methods for early diagnosis of ovarian cancer are constantly being sought. Modern diagnostic methods would enable earlier detection of ovarian cancer at a less advanced stage, thereby improving prognosis. Such investigations could include the assessment of tumor markers in biological samples. For example, the preliminary utility of tumor markers (evaluated in peripheral blood) has been demonstrated in the diagnosis of breast[6,7] and gynecologic cancers,[8–10] including ovarian cancer.[11,12] In addition to early detection of cancer, tumor markers can also be used to

assess prognosis and monitor the clinical course of the disease.[13–16] Among the groups of molecules considered to be potential markers for ovarian cancer, matrix metalloproteinases (MMPs) are of particular interest.[8,17–19]

Ovarian Cancer: An Overview
Classification and Symptoms of Ovarian Cancer

Ovarian cancers originate from three types of cells— epithelial cells, germ cells or from sex chord and stromal cells. As mentioned in the introduction, epithelial malignancies (ovarian carcinoma or ovarian epithelial cancer) account for the majority of lesions diagnosed in patients. It is important to note that non-epithelial malignancies have a much better prognosis and are less invasive than carcinomas. Ovarian epithelial cancer is a heterogeneous disease. It can be subdivided into high-and low-differentiated serous, endometrioid, clear cell, and mucinous carcinomas based on histopathologic, molecular, and immunologic findings. The different types of ovarian carcinomas differ in pathogenesis, prognosis, and response to chemotherapy. The most commonly diagnosed type, which also has the highest mortality rate, is high-grade serous ovarian carcinoma, which accounts for 70–80% of ovarian cancer-related deaths. The second most common type is endometrioid carcinoma, which has a better prognosis than the high-grade serous type.[1–3,17,20–22]

Because of its asymptomatic course, ovarian cancer is often called the "silent killer". Most patients are in stage III or IV at the time of diagnosis according to the International Federation of Gynecology and Obstetrics (FIGO) classification (see Table 1). Due to the lack of anatomical barriers around the ovary, exfoliated cancer cells easily enter the peritoneum, where they are distributed through the peritoneal fluid to the abdominal organs and then further to distant organs. This results in the formation of numerous metastatic foci—mainly in the liver, lymph nodes, bones, brain, and lungs. Metastasis to the intestines, resulting in their obstruction, is particularly life threatening. It is estimated that bowel obstruction is the most common cause of death in the course of ovarian cancer.[2,17,20,23–26]

Nonspecific and minimal symptoms appear in the advanced stages of ovarian cancer and are usually not directly related to the reproductive system. Patients mainly report abdominal and pelvic pain or discomfort, which is most often confused with other complaints, such as indigestion, irritable bowel syndrome, or menstrual pain. Other gastrointestinal symptoms include bloating, early satiety, increased abdominal girth, and loss of appetite. Some of the other commonly reported symptoms include back pain, general fatigue, and urinary symptoms, such as frequent or excessive urination. Typical gynecological symptoms include menstrual disorders, postmenopausal bleeding, and pain or bleeding during intercourse.[4,29,30] As the disease progresses, some patients may experience intestinal obstruction (as previously mentioned) or ureteral obstruction, which can result in renal failure. The development of ascites is associated with a poor prognosis.[2,24,31] It should also be mentioned that the presence of cancer cells can induce paraneoplastic syndromes, such as subacute cerebellar degeneration, dermatomyositis, migratory thrombophlebitis (Trousseau syndrome), disseminated intravascular coagulation, and hemolytic anemia.[4,32] The symptoms and complications of ovarian cancer, as well as the most common locations of metastases, are presented in Figure 1.

Selected Risk and Protective Factors for Ovarian Cancer
Age

Age is one of the most important risk factors for ovarian cancer. In general, the risk of ovarian cancer increases with age. The disease mainly affects postmenopausal women; 50% of cases are diagnosed after the age of 65, while ovarian cancer

Table 1 FIGO's Staging Classification for Ovarian Cancer

Stage I: Tumor confined to ovaries or fallopian tube(s)
Stage II: Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
Stage IV: Distant metastasis excluding peritoneal metastases

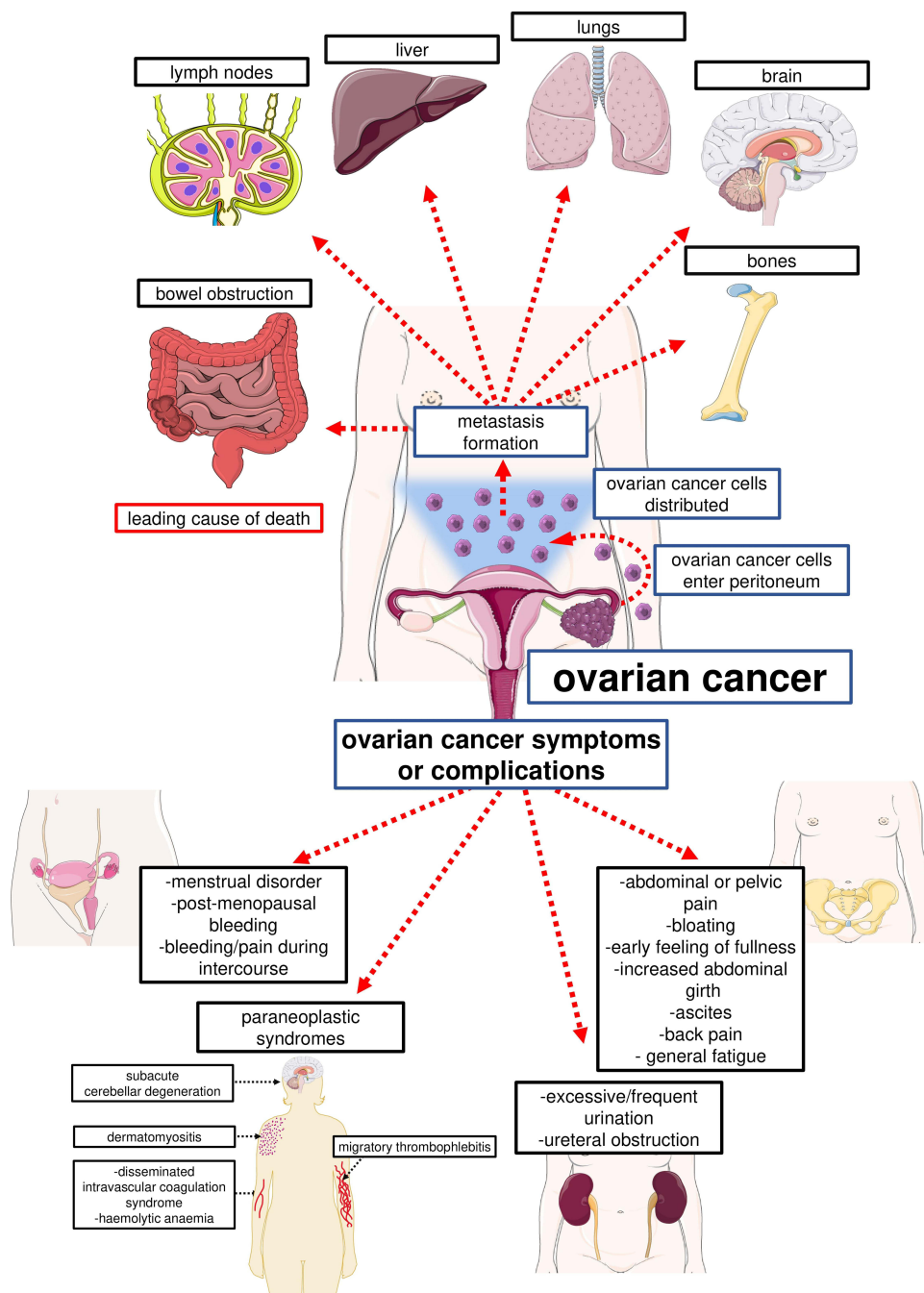**Note**: Data adapted from Javadi et al,[21] Prat et al,[27] and Berek et al.[28]

Figure 1 Symptoms and complications of ovarian cancer and the most common sites of metastatic foci.

is rare before 40 years of age. Among all types of ovarian cancer in the postmenopausal period, high-grade serous ovarian carcinoma is the most common and, as discussed earlier, has the poorest prognosis. It is also notable that ovarian cancer has a worse prognosis in older patients compared to younger patients, mainly due to less aggressive treatment approaches and higher disease stage at the time of diagnosis.[2,5,33,34]

Genetic Factors

Besides age, genetics are considered the second most important risk factor for ovarian cancer. Genetic predisposition to ovarian cancer manifests as hereditary ovarian cancer, hereditary ovarian and breast cancer syndrome, and hereditary nonpolyposis colorectal cancer (Lynch syndrome). Hereditary ovarian and breast cancer syndrome is the most

common.[27,34] Patients whose mother and/or sister(s) also suffer from ovarian cancer are particularly vulnerable. Interestingly, a family history of breast and uterine cancer in a mother or sister also increases a woman's likelihood of developing ovarian cancer. According to the literature, over 50% of genetically determined ovarian cancers are caused by BRCA1 and BRCA2 gene mutations.[1,5,35,36] The BRCA1 and BRCA2 genes are classified as tumor suppressor genes; functional BRCA1/BRCA2 proteins are responsible for repairing DNA double helix breaks through the process of homologous recombination. BRCA1/BRCA2 mutations are inherited in an autosomal dominant manner; however, they function as recessive genes at the cellular level. Loss of function of these genes results in genome instability and, consequently, neoplastic cellular transformation.[37–40] The estimated average risk of developing ovarian cancer is 20–50% in patients with a BRCA1 mutation and 5–25% in patients with a BRCA2 mutation. According to the literature, patients with BRCA1/BRCA2 mutations most often develop high-grade serous carcinoma. However, it should be noted that ovarian cancer patients with mutations in the BRCA genes have a better prognosis than patients with other types of mutations. In addition, BRCA2 gene mutation patients have a better prognosis than BRCA1 gene mutation patients, mainly because the former respond better to cisplatin therapy. A protective method in patients with BRCA1/BRCA2 gene mutations is prophylactic salpingo-oophorectomy, which has been shown to reduce the risk of ovarian cancer by 75%.[1,5,41,42]

Lynch syndrome is caused by an autosomal dominant mutation of the genes responsible for DNA repair, including MHL1, MSH2, MSH6, and PMS2. This syndrome is usually associated with an increased risk of developing colorectal cancer; however, patients also tend to develop ovarian cancer.[33,35,43–45] It is estimated that 10–15% of genetically determined ovarian cancer cases are associated with Lynch syndrome,[5,20,46] and the lifetime risk of ovarian cancer in Lynch syndrome patients is estimated to be 8%.[46] The most common histological subtype of cancer in these patients is endometrioid carcinoma.[47] However, patients have a relatively good prognosis, which is related to earlier detection—usually stage I or II—according to FIGO (see Table 1). For the patients with Lynch syndrome, salpingo-oophorectomy is a prophylactic approach.[44,46,48]

Many other mutations may increase the risk of developing ovarian cancer. These include mutations in the TP53 (Li-Fraumeni syndrome),[20,49,50] STK11 (Peutz-Jeghers syndrome), BRIP1,[51] RAD51C,[52] and PALB2 genes.[53] These mutations have not been studied as thoroughly as mutations in the BRCA1/BRCA2 and DNA repair genes.

Gynecologic and Gynecologic-Related Factors

In addition to genetic determinants, there are many other risk factors for ovarian cancer that have been studied to varying degrees. The vast majority are associated with pathologies within the reproductive system. The impact of endometriosis on ovarian cancer risk is particularly well understood. Because endometrial lesions tend to become malignant, patients with endometriosis, especially those located within the ovaries, have a higher risk of developing ovarian cancer; this risk is 50% higher than in the general population.[34,54] Ovarian cancer in patients with endometriosis is known as endometriosis-associated ovarian cancer (EAOC). Histologically, the most common EAOC tumor types are clear cell, endometrioid, and low-grade serous carcinoma. The pathological mechanism of the formation of a neoplastic lesion from an endometriosis focus is complex and includes oxidative stress, inflammatory processes, estrogen effects (hyperestrogenism), hemorrhages, and somatic mutations in the PIK3CA, PTEN, and ARID1A genes.[5,55–57] In general, patients with EAOC have a good prognosis as long as they are diagnosed early enough.[58]

According to a few scientific reports, benign ovarian cysts can be precursors to malignant lesions. Although most cysts disappear spontaneously, there is a small risk of developing ovarian cancer from benign lesions. In postmenopausal patients, the likelihood of a malignant lesion developing from a simple cyst is estimated at 0.3%. With complex cysts, this risk increases to 36%.[59,60] Other documented risk factors for ovarian cancer include pelvic inflammatory disease. Patients with recurrent pelvic inflammatory disease have been shown to have a higher risk of developing ovarian cancer.[61–63] One cause of pelvic inflammatory disease is *Chlamydia trachomatis* infection; patients with a history of *C. trachomatis* infection have been shown to have a higher risk of developing ovarian cancer.[64,65]

The role of polycystic ovary syndrome (PCOS) in the development of ovarian cancer is controversial. Since PCOS patients have ovulatory-free cycles, some researchers assert that they should have a lower risk of ovarian cancer (the effect of ovulation on ovarian cancer risk will be described later).[66,67] Conversely, a study by Schildkraut et al[68] found

a 2.5-fold increased risk of ovarian cancer in PCOS patients, especially in those with elevated body mass index (BMI) and no oral contraceptive use. However, it should be noted that the study was conducted on a small group of patients. Far more studies suggest that PCOS does not increase the risk of ovarian cancer.[69,70]

Other debatable factors associated with ovarian cancer risk include the use of talc, which is an ingredient in baby powder, and feminine hygiene products. A study by Cramer et al[71] determined that the regular application of talc to the genital area was associated with an increase in overall ovarian cancer risk. However, according to O'Brien et al,[72] there is no association between talc use and increased ovarian cancer risk. Because talc can be contaminated with carcinogens, such as asbestos and quartz, more research on the potential links between talc and the development of ovarian cancer is warranted.[34,73]

Besides the factors that increase the risk of ovarian cancer, there are numerous protective factors, including tubal ligation, oral contraceptive use, and pregnancy.[5,34] Large studies have determined that tubal ligation reduces the risk of ovarian cancer. The greatest decrease in risk was observed for endometrioid ovarian carcinoma. It is likely that ligated fallopian tubes provide a mechanical barrier to carcinogens.[33,74,75]

According to the "Incessant Ovulation Theory", uninterrupted ovulation may contribute to increased ovarian cancer risk. During ovulation, the ovarian epithelium is damaged and then undergoes regeneration. Repeated damage to the ovarian epithelium translates into the possibility of errors during the replication process and resulting DNA damage, which in turn increases the risk of cancerous transformation.[5,22,76,77] Therefore, any factor that inhibits ovulation might contribute to a decrease in ovarian cancer risk; one such factor is oral contraceptive use. According to the literature, oral contraceptive use reduces the risk of ovarian cancer regardless of its type.[5,33,78–82] The greatest protective effect of oral contraceptive use is observed in women taking the medication for a longer period of time— the risk of getting the disease decreased with the duration of pill use.[78,80] It is estimated that in women taking the pill for 15 years, the risk of developing ovarian cancer decreases by 70%. Interestingly, a protective effect was already observed with lower doses of the drug.[78] Positive effects of hormonal contraception were also found in BRCA1/ BRCA2 mutation carriers. In female carriers, long-term use translated into a reduced risk of ovarian cancer.[33,83]

Pregnancy is another confirmed protective factor. Both term and non-delivered pregnancies reduce the risk of ovarian cancer. It has been shown that an increase in the number of pregnancies translated into a further decrease in the risk of ovarian cancer.[5,22,33,34,84] However, the exact mechanism of the protective effect of pregnancy on ovarian cancer risk is not well understood. In addition to inhibition of ovulation during pregnancy, one of the postulated reasons is the high concentration of progesterone that occurs physiologically in the tissues of pregnant women to maintain pregnancy.[22,84] This theory is supported by in vitro studies by Yu et al[85] and Lima et al[86] in which progesterone inhibited proliferation, migration, and invasion of ovarian cancer cells and also induced apoptosis.

Lactation is directly related to pregnancy. Breastfeeding is one of the better documented factors in reducing the risk of ovarian cancer. In fact, a stronger protective effect was observed with longer duration of breastfeeding.[5,33,87–89] According to a study by Babic et al,[90] breastfeeding for 12 months or longer reduced the risk of ovarian cancer by 34%; this relationship was demonstrated mainly for high-grade serous and endometrioid carcinomas. As in the case of pregnancy, the protective mechanism of breastfeeding consists mainly of the induction of ovulatory-free cycles and probably the inhibition of luteinizing hormone release, which has been postulated to be involved in the pathogenesis of ovarian cancer.[34]

Lifestyle Factors

Numerous lifestyle-related factors are associated with decreased or increased risks in the development of ovarian cancer. An association between obesity and increased ovarian cancer risk has been demonstrated. Women with a higher BMI were more likely to develop ovarian cancer than women in the healthy weight range.[5,34,91,92] Interestingly, women who had a high BMI in early adulthood also had an increased risk of ovarian cancer in later life.[91] Furthermore, obesity translated into a worse prognosis in the course of ovarian cancer.[34,93,94] The pathogenesis of obesity-related ovarian cancer most likely results from changes in the bioavailability of active compounds in female tissues. Obese women have an increased availability of compounds with potentially procarcinogenic properties, including leptin, inflammatory mediators, androgens, and estrogens, while a decrease in progesterone (as mentioned earlier) who had a protective effect on the development of ovarian cancer.[5,34,91,94]

Although cigarette smoking is one of the most important factors that increases the risk of several types of cancer, no significant association has been found between smoking and the overall risk of ovarian cancer.[95,96] However, it should be noted that female smokers have an increased risk of mucinous carcinoma.[34,96–98] Furthermore, smoking patients with ovarian cancer had a worse prognosis compared to non-smoking ovarian cancer patients.[34,94]

Alcohol is another factor linked to an increased risk of various types of cancer. In the case of ovarian cancer, studies have not confirmed a link between alcohol consumption and an increased likelihood of developing this type of cancer.[5,33,99,100]

The effect of diet on increasing or decreasing cancer risk has been known for many years; individual nutrients also affect ovarian cancer risk. The main foods with a protective effect include fresh fruits and vegetables, which is mostly due to their antioxidant properties.[34,101–103] At the same time, consumption of salted and canned vegetables has been shown to increase the likelihood of developing ovarian cancer.[101,102] The effect of dairy products depends on their type—consumption of milk, sour milk products, and yogurt increased the risk of ovarian cancer, while an inverse relationship was observed with cheese.[104] It has also been shown that patients who have a diet high in fat (especially animal fat or saturated fat and cholesterol) were more likely to develop ovarian cancer.[34,103] A similar relationship was demonstrated for smoked and fried foods.[101]

Matrix Metalloproteinases—Physiological Role and Involvement in Pathological States

Matrix metalloproteinases (MMPs) comprise a group of proteolytic enzymes that are similar in structure whose enzymatic activity depends on zinc ions.[17,105–114] Twenty-eight enzymes of the MMP family have been identified in vertebrates. However, only 23 MMPs are expressed in humans.[107,113,115] Interestingly, MMP-23 exists in two isoforms that are encoded by two separate genes—MMP-23A and MMP-23B.[105,114,116] Based on their specificity to the degraded substrate, MMPs can be divided into six groups: (1) gelatinases; (2) collagenases; (3) stromelysins; (4) matrilysins; (5) membrane-type MMPs; and (6) other MMPs.[110,113,116–118] The division of MMPs with examples is shown in Figure 2.
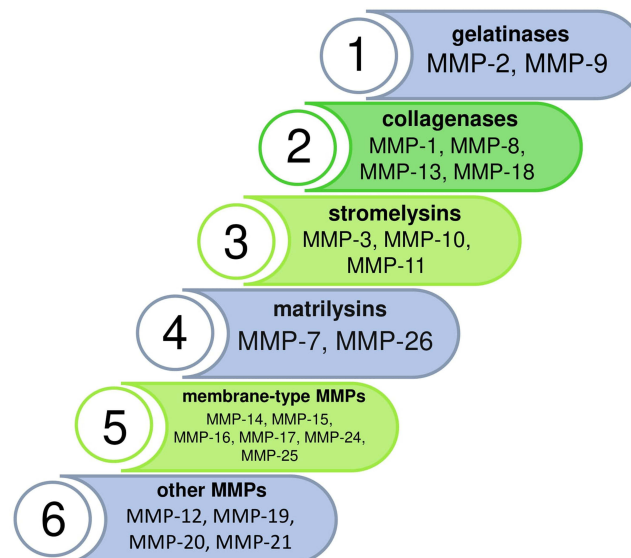

Figure 2 Division of matrix metalloproteinases.
Abbreviations: MMP-1, Metalloproteinase-1; MMP-2, Metalloproteinase-2; MMP-3, Metalloproteinase-3; MMP-7, Metalloproteinase-7; MMP-8, Metalloproteinase-8; MMP-9, Metalloproteinase-9; MMP-10, Metalloproteinase-10; MMP-11, Metalloproteinase-11; MMP-12, Metalloproteinase-12;MMP-13, Metalloproteinase-13; MMP-14, Metalloproteinase-14; MMP-15, Metalloproteinase-15; MMP-16, Metalloproteinase-16; MMP-17, Metalloproteinase-17; MMP-18, Metalloproteinase-18; MMP-19, Metalloproteinase-19; MMP-20, Metalloproteinase-20; MMP-21, Metalloproteinase-21; MMP-24, Metalloproteinase-24; MMP-25, Metalloproteinase-25; MMP-26, Metalloproteinase-26; MMPs, Matrix metalloproteinases.

MMPs are produced by various cell types, including smooth muscle cells, leukocytes, platelets, fibroblasts, and endothelial cells.[105–113] The primary function of MMPs is to maintain physiological tissue homeostasis by digesting components of the extracellular matrix. In addition to the degeneration of extracellular matrix components, MMPs are also involved in the degradation of other proteolytic enzymes (including other MMPs), protease inhibitors, blood clotting factors, cytokines, antimicrobial peptides, growth factors, adhesion molecules, and membrane-bound receptors.[17,106–113,118,119] They also mediate the formation of chemokines, growth factors, and other biologically active peptides from their inactive precursors.[109]

MMPs are secreted into the environment as inactive zymogens known as proMMPs. ProMMPs are maintained in an inactive form by binding between a conserved cysteine in the propeptide domain of the molecule and a zinc ion in the catalytic center. ProMMPs are activated by breaking the chemical bond between the cysteine amino acid and the zinc ion, which can occur through three different mechanisms. The first involves limited proteolysis, resulting in the removal of the prodomain. This process occurs through the activity of other proteolytic enzymes, such as plasmin, furin, chymase, or other MMPs, including MMP-3, MMP-10, and MMP-14.[105,107,111,113,115,119] In the second mechanism, proMMPs are activated by reactions between the cysteine amino acid in the propeptide domain and alkylating agents, heavy metal ions, or reactive oxygen species. The third mechanism of MMPs activation occurs through allosteric reconformation of the prodomain.[105,106,119,120]

The proteolytic activity of MMPs is regulated by tissue inhibitors of metalloproteinases (TIMPs). TIMPs bind covalently to a given MMP or its precursor form, thereby inhibiting its activity. Four types of TIMPs have been identified: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. The different types of TIMPs differ in their affinity for MMPs.[105,106,111,113,114,118,121] Interestingly, MMPs activity can also be controlled by non-specific inhibitors, such as α2-macroglobulin, α1-antitrypsin, β-amyloid precursor protein, tissue factor pathway inhibitor-2, and serine proteinase inhibitor.[105,113,117]

MMPs have multiple physiological roles, including regulation of cellular processes related to differentiation and proliferation, apoptosis, and induction of inflammatory or immune responses. These enzymes are involved in wound healing, tissue remodeling, ovulation, and restoration of the endometrium during the menstrual cycle. During fetal development, MMPs are involved in embryogenesis and organogenesis, with particular emphasis on the development of the cardiovascular, respiratory, and musculoskeletal systems. They are also essential during the final stages of pregnancy and childbirth.[105–107,109,110,113,117,118,122]

Physiologically, the activity of MMPs is maintained in a state of equilibrium; if their activity becomes dysregulated, these enzymes can contribute to the onset and progression of various pathological conditions. Dysregulation of MMPs has been shown to be associated with the progression of several cardiovascular (aortic and intracranial aneurysms, arteriosclerosis, coronary artery disease, pathological myocardial remodeling, and hypertension),[107,111,113,117,123,124] nervous (Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis),[107,111,113,125,126] excretory (renal fibrosis, chronic kidney disease, and diabetic nephropathy),[111,127,128] respiratory,[107,111,113,129,130] musculoskeletal (osteoarthritis and osteoporosis),[107,110,118,131] and liver diseases (hepatic fibrosis, cirrhosis, and portal hypertension).[107,111,132]

MMPs also play an important role in all stages of carcinogenesis.[122] Among other functions, MMPs affect tumor cell proliferation, migration, and invasion, stimulate angiogenesis, and induce epithelial–mesenchymal transition within the cancerous lesion.[111,112,114,118,121,122,133] In the early stages of cancer, MMPs induce DNA damage and resultant genomic instability.[134,135] For example, MMP-2 localizes in the cell nucleus and degrades proteins responsible for repairing DNA damage.[136] At the stage of tumor progression, a particularly important role of MMPs is the aforementioned stimulation of angiogenesis and lymphangiogenesis, which has been shown to enable further growth of the tumor mass.[112,116,135,137] In the later stages of the disease, MMPs activity has been associated with the formation of metastatic foci, mainly due to their proteolytic properties that enable digestion of the extracellular matrix.[111,112,135,138] The role of MMPs in the process of carcinogenesis is shown in Figure 3.

Metalloproteinases in Ovarian Cancer
Gelatinases—MMP-2 and MMP-9

MMP-2 expression is found in physiological ovarian tissue,[14,16] whereas MMP-9 expression is low[14,139] or undetectable.[139,140] Expression of MMP-2[15,141–147] and MMP-9[14,140,147,148] is found in ovarian cancer samples. Expression of MMP-2 and MMP-9 is found directly in cancer epithelial cells,[14,15,141–148] within the stroma of the
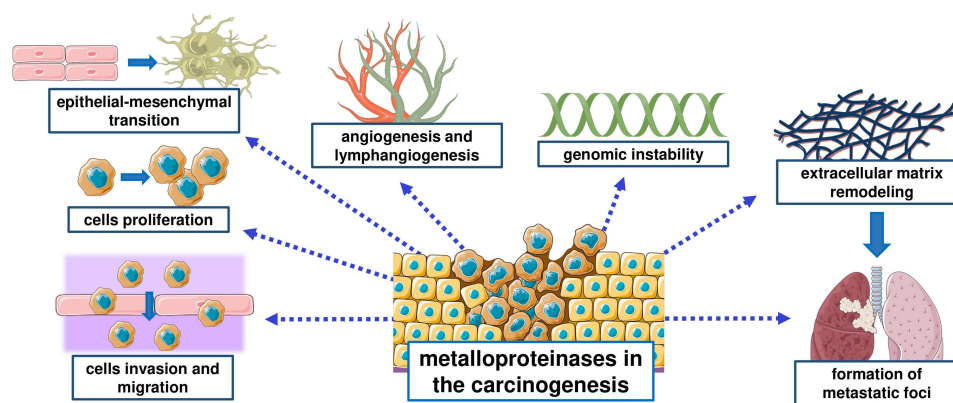
Figure 3 Multidirectional role of MMPs in carcinogenesis.

tumor lesion,[15,141–143,145,147] and in metastatic foci.[141] Expression of MMP-9 is higher in cancer compared to benign lesions.[139,142] Expression of MMP-2[145–147] and MMP-9 is found in all histological types of ovarian carcinoma.[146–148] According to most reports, there are no differences in MMP-2 and MMP-9 expression between the different histological types of ovarian carcinoma.[14,15,139] However, according to Jeleniewicz et al[146] the highest expression of MMP-2 was found in the serous ovarian carcinoma type and chemotherapy-sensitive tumors. Additionally, a single study determined that the highest expression of MMP-9 was in the high-grade serous ovarian carcinoma.[147] MMP-2 expression levels were independent of disease stage, tumor size, and treatment effects. However, there was a correlation between MMP-2 expression and the tendency of ovarian cancer to recur, as well as the presence of metastatic lesions.[15] In contrast to MMP-2, MMP-9 expression was closely related to the ovarian cancer stage according to the FIGO classification; it was higher in stages III and IV than in less advanced stages.[14,139,140] Furthermore, MMP-9 levels were higher in patients with established metastatic foci than in patients without metastasis.[142,148] Levels of MMP-9 expression have also been shown to be positively correlated with the number of vasculogenic-like networks formed in cancerous tissue.[139] The formation of vasculogenic-like networks is associated with the so-called "vascular mimicry phenomenon", which involves the transformation of cancer cells into endothelial-like cells and the formation of vascular-like structures. In addition to providing for the metabolic needs of the growing tumor lesion, these structures have been shown to provide an alternative pathway for cancer cell extravasation and subsequent metastasis.[149–151]

The relationship between MMP-2 expression and patient prognosis is controversial. MMP-2 expression in cancer epithelial cells,[141,147] stroma, and metastatic foci[141] was associated with poorer patient prognosis. However, as reported by Ekinci et al,[15] Vos et al[145] and Jeleniewicz et al,[146] Maneti et al,[152] there was no association between MMP-2 expression in cancer epithelial cells and patient prognosis. The presence of MMP-2 in the stroma of the lesion is another matter of debate. Morales-Vásquez et al[147] and Maneti et al[152] stated that this MMP has a protective effect in ovarian cancer patients, while Ekinci et al[15] reported that the survival time of patients expressing stromal MMP-2 was shorter. The relationship between MMP-9 expression and patient survival is unclear. According to Hu et al,[14] the mean survival time of ovarian cancer patients expressing MMP-9 was significantly shorter than that of patients with negative MMP-9 expression, while a study by Sillanpää et al[148] described an inverse relationship.

Although the preliminary usefulness of gelatinases determined from peripheral blood has been determined in patients with different types of cancers,[153,154] studies of MMP-2 and MMP-9 in patients with ovarian cancer are incomplete and inconclusive. Serum MMP-2 levels were lower in ovarian cancer patients than in healthy women. However, there was no difference in the levels of this MMP between patients with ovarian cancer and women with benign lesions.[155] In contrast to MMP-2, the serum and plasma levels of MMP-9 were higher in women with ovarian cancer than in healthy patients or those with benign lesions.[14,152,156,157] Serum MMP-2 levels were not dependent on ovarian cancer stage according to FIGO,[155] while MMP-9 levels were higher in patients with stage III and IV disease according to FIGO than in women with stage I and II disease.[156,157] However, there was no correlation between MMP-9 levels and the histological types of ovarian carcinoma.[14,156] Additionally, elevated serum MMP-9 levels were

found in women who were insensitive to chemotherapy or had ascites or metastatic foci.[14,156] Importantly, Ławicki et al[157–159] investigated plasma levels of MMP-9 and the most common marker in ovarian cancer (CA-125) in two independent studies and reported that the highest diagnostic sensitivity values for ovarian cancer were obtained when these two markers were evaluated together. In addition, MMP-9 levels decreased in patients after surgery, indicating the potential use of this enzyme to assess the effectiveness of surgical procedures. The potential of MMP-2 and MMP-9 to predict the prognosis of ovarian cancer patients has not yet been thoroughly researched. A single study demonstrated that there was no relationship between plasma MMP-2 and MMP-9 levels and prognosis.[152]

Interestingly, there is a single report of elevated MMP-2 and MMP-9 concentrations in the urine of women with ovarian cancer in whom the routine marker CA-125 remained within reference norms.[160] This indicates that MMP expression levels and blood concentrations may not be the only parameters that potentially have diagnostic value.

Collagenases—MMP-1, MMP-8, MMP-13, and MMP-18

The expression or activity of collagenases in healthy ovarian tissue varies by type. MMP-1 activity[161] and MMP-18 expression[162] have been identified in ovarian tissue collected from healthy women. MMP-13 expression was not found in physiological ovarian tissue,[16] and MMP-8 expression has not been studied. The expression of MMP-1, MMP-8, and MMP-13 was found in ovarian cancer samples, while the presence of MMP-18 has not been investigated.[16,163–166] According to Behrens et al,[163] MMP-1 expression was higher in ovarian cancers compared to benign lesions. The expression of the other collagenases in benign lesions has not yet been studied. The relationship between collagenase expression levels and prognosis has been studied using MMP-8 and MMP-13 as examples —higher expression of these collagenases was associated with poorer prognosis.[16,165] Patients who were at higher stages of ovarian cancer exhibited higher MMP-8 tissue levels. Moreover, higher expression of MMP-8 was associated with higher expression of MMP-9, whose diagnostic significance was discussed in the previous section.[165] MMP-13 expression was not related to disease stage or whether the cancer occupied one or two ovaries.[166]

The activity of individual collagenases was also examined in fluids collected from ovarian cysts. MMP-1 and MMP-13 activity in the ovarian cysts was determined to be low, and there was no difference in MMP-1 activity between benign and malignant cysts. MMP-8 activity was higher in malignant cysts than in benign cysts.[164]

A single study reported on MMP-13 levels in peritoneal fluid from patients with advanced forms of ovarian cancer (FIGO stage III or IV); patients with higher MMP-13 levels had a worse prognosis than patients with lower MMP-13 levels.[167] There are currently no studies on the diagnostic utility of collagenases measured in peripheral blood in ovarian cancer patients, but preliminary studies indicate that they potentially have diagnostic value in other types of cancer, such as gastric cancer[168] and skin cancer.[169]

Stromelysins—MMP-3, MMP-10, and MMP-11

As with collagenases, the expression of stromelysins in physiological ovarian tissue depends on their type. MMP-3 is found in physiological ovarian tissue, but MMP-10 is not expressed.[16,170] To date, MMP-11 expression in physiological ovarian tissue has not been studied. Patients with ovarian cancer express all three of these stromelysins.[16,166,171,172] Interestingly, high MMP-11 expression was associated with higher tissue expression of other MMPs, including MMP-2 and MMP-13.[166] The potential utility of these two enzymes in ovarian cancer was described in earlier sections of this article. In the cases of MMP-3 and MMP-11, higher expression was found at higher stages according to the FIGO classification,[166,171,173] while there was no correlation between the levels of these stromelysins in cancerous tissue and patient prognosis.[16,172] In contrast, high MMP-10 expression was associated with a better prognosis for patients at stages III and IV.[16]

There is very limited research on the potential utility of stromelysins as tumor markers in peripheral blood. A single study reported that patients with ovarian cancer had higher MMP-3 levels compared to women with benign lesions. Higher MMP-3 levels were found in women in more advanced stages according to the FIGO classification. Furthermore, patients with high baseline MMP-3 levels had a worse prognosis than patients with lower levels of this enzyme.[174]

Matrilysins—MMP-7 and MMP-26

Low expression of MMP-7 was found in physiological ovarian tissue.[175–177] High or low expression of MMP-26 was also observed, depending on the structure of the ovary.[178] Samples from ovarian cancer patients exhibited the expression of both of these matrilysins.[16,143,144,166,175,177–179] MMP-7 was detected in the stroma of a cancerous lesion[143] and in metastatic foci of ovarian cancer.[177] MMP-7 expression was the same in the metastatic foci as in the primary lesion.[177] Interestingly, MMP-7 was identified in the mucin of mucinous ovarian carcinoma, indicating that MMP-7 is produced by cancer gland cells.[177] Data on MMP-7 expression in ovarian cancer compared to benign lesions are scarce and contradictory. According to Wang et al,[176] higher MMP-7 expression was found in patients with serous ovarian carcinoma compared to benign lesions; however, Brun et al[143] documented higher MMP-7 expression in benign lesions compared to serous ovarian carcinoma. To the best of our knowledge, no studies have compared MMP-26 expression between benign and malignant ovarian lesions. No correlation was found between MMP-7 expression and ovarian cancer stage according to the FIGO classification,[166] while MMP-26 expression was dependent on FIGO stage, with higher expression levels observed in stages III and IV compared to stage I.[178]

A study by Sillanpää et al[177] suggests a potentially protective role for MMP-7 in ovarian cancer. Patients with high expression of this MMP in cancerous tissue had a better prognosis in terms of 10-year disease-related survival rate and recurrence-free survival time. The protective properties of MMP-7 seem to confirm the results presented in the same study, which state that low expression of MMP-7 was associated with advanced tumor stage, high histological tumor grade, and large primary residual tumor. The study by Sillanpää et al[117] is not supported by the results of Zeng et al,[16] who found no relationship between MMP-7 expression and prognosis. At present, no relationship has been demonstrated between MMP-26 expression levels and prognosis.[16]

Some studies have noted the preliminary potential of MMP-7 as a biomarker in peripheral blood samples. In ovarian cancer patients, plasma or serum MMP-7 levels were higher than in healthy subjects and those with benign lesions.[155,179–181] No relationship was found between serum MMP-7 levels and tumor stage, tumor grade, and presence of metastasis or ascites,[155,179] but a relationship was shown between MMP-7 levels and primary tumor size.[179] Notably, MMP-7 levels after surgery and chemotherapy were reduced, which suggests the possibility of using this MMP to evaluate the efficacy of ovarian cancer treatment in the future.[155,179] According to Będkowska et al,[181] MMP-7 had comparable diagnostic sensitivity and specificity values and negative and positive predictive values as two routine ovarian cancer markers (CA-125 and HE4). In addition, preliminary analyses indicate the possibility of detecting ovarian cancer at earlier stages using simultaneous determination of MMP-7 and CA-125.[180] To the best of our knowledge, no studies have evaluated the levels or diagnostic utility of MMP-26 in the serum or plasma of ovarian cancer patients. However, elevated levels of this MMP are found in other types of cancer, including breast cancer[18] and prostate cancer.[182]

Membrane-Type MMPs—MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, and MMP-25

Research on the expression of membrane-type MMPs in physiological ovarian tissue is inconsistent. On one hand, some scientific reports have confirmed the expression of MMP-14, MMP-15, MMP-16, MMP-24, and MMP-25 in normal ovarian tissue.[183,184] On the other hand, a study by Testuri et al[185] failed to determine whether membrane MMPs were expressed in physiological ovarian tissue. Similar observations for MMP-25 were made by Zeng et al,[16] but the study was conducted on a small number of samples (n = 3). In ovarian cancer, the expression of MMP-14,[13,16,142,144,166,184–187] MMP-15,[16,185] MMP-16,[16,166,185,188] MMP-17, MMP-24,[16,166,185] and MMP-25[16,166] was confirmed by numerous studies. Both epithelial and stromal expression was demonstrated for MMP-14.[13,142,145,186] Epithelial and stromal MMP-14 expression was associated with ascites and lymph node involvement, whereas high mRNA levels in the epithelium, in particular, translated to the development of distant metastatic foci.[13] Interestingly, an inverse relationship with CA-125 was observed for MMP-14 expression. Tumors with high MMP-14 expression simultaneously had low CA-125.[189] A study by Sakata et al[142] determined that benign lesions had lower MMP-14 expression than cancer; however, according to Testuri et al,[185] there was no expression of MMP-14 or other membrane MMPs in nonmalignant ovarian lesions. Therefore, further studies are needed to clearly ascertain the potential of membrane MMPs as auxiliary markers

for differentiating between benign and malignant lesions. The relationship between FIGO stage and expression of membrane-type MMPs is a matter of debate. According to Escalona et al,[173] mRNA levels of MMP-14 increased with higher FIGO classification stages. On the contrary, Wang et al[166] found no relationship between MMP-14 expression and ovarian cancer stage. According to a single study, there was no relationship between MMP-17 and MMP-24 expression and FIGO stage. However, MMP-16 and MMP-25 expression was higher in FIGO stages III and IV than in less advanced stages.[166]

A few studies have reported an association between membrane MMP expression and prognosis. According to Kamat et al,[13] patients with high epithelial and stromal MMP-14 expression had low disease-related survival rate values; the lowest disease-related survival rate values were among women with high MMP-14 expression found only in cancerous epithelium. Patients with moderate MMP-14 expression in the epithelium accompanied by low stromal expression had the best prognoses.[13] In addition, Wang et al[166] determined that high levels of mRNA for MMP-14 in ovarian cancer were associated with a poorer prognosis. However, it should be noted that according to Zeng et al,[16] MMP-14 expression was not associated with patient survival. A similar relationship was found for MMP-15,[166] MMP-16,[16] MMP-17,[16,166] and MMP-24.[166] Interestingly, high expression of MMP-25 was associated with longer overall survival.[16]

To the best of our knowledge, only a single study to date has suggested that MMP-14 can be used as a blood-based marker for ovarian cancer patient. MMP-14 concentrations were higher in women with ovarian cancer compared to healthy patients and those with benign lesions.[190] However, the concentrations and potential utility of other membrane MMPs as markers in peripheral blood in patients with ovarian cancer have not yet been investigated.

Other Types of MMPs—MMP-12, MMP-19, MMP-20, and MMP-21

There is limited research on the other MMPs. No MMP-12 expression was found in normal ovarian tissue.[16] Expression of MMP-19, MMP-20, and MMP-21 has not yet been studied. MMP-12, MMP 19, MMP-20, and MMP-21 mRNA was found in serous and endometrioid ovarian carcinoma.[16,166] According to Wang et al,[166] there was no correlation between MMP-12, MMP-19, MMP-20, and MMP-21 mRNA levels and FIGO stage. Differences were found between the expression of individual MMPs and prognosis. High levels of MMP-12 expression in stage III or IV patients were associated with better overall survival. The same study simultaneously found that MMP-19, MMP-20, and MMP-21 expression was not associated with prognosis.[16] However, it should be noted that Wang et al[166] determined that high MMP-19 and MMP-20 expression was associated with poor overall survival and that these two MMPs could serve as independent factors to predict poor prognosis in ovarian cancer patients. The poor prognosis of female patients has been shown to be due to a complex mechanism of action, studied in vitro, in which MMP-19 and MMP-20 induced resistance to anti-cancer drugs and stimulated cancer cell invasion.[166]

To the best of our knowledge, no studies have established the potential of other MMPs as peripheral blood markers in ovarian cancer patients. A single study of colon cancer patients determined that MMP-12 has potential as a novel tumor marker.[191] It is unfortunate that the potential of MMP-19, MMP-20, and MMP-21 as tumor markers has not been determined by any oncology studies. Therefore, future investigations of this group of enzymes should be conducted to evaluate their potential utility, not only in ovarian cancer patients, but also in other types of cancer. A representation of the most significant characteristics of MMPs is presented in Table 2

Conclusion

Ovarian cancer is one of the most common gynecologic malignancies, and many interrelated factors contribute to its prevalence. Due to its usually asymptomatic or minimally symptomatic course, it is most often detected at an advanced stage, which translates into an unfavorable prognosis. Considering the increasing number of cases and its insidious nature, it is vital to search for new ways to enable earlier diagnosis of ovarian cancer. Additionally, besides early detection, it is necessary to properly control its progress and assess its prognosis. It might be possible to measure these tumor markers in different biological samples as diagnostic parameters. This article summarized the potential role of extracellular MMPs in the diagnosis, monitoring, and prognosis assessment of ovarian cancer patients.

MMPs are involved in all stages of carcinogenesis, and their role and potential utility in ovarian cancer remains controversial. Most currently known MMPs are expressed in ovarian cancer, and high expression of some of them (eg,

Table 2 The Most Significant Properties of MMPs Groups Found in Tissue Studies and Body Fluids

Gelatinases		
MMP	**Results**	**References**
MMP-2	**Research in tissues** -Expression was found in: physiological ovarian tissue, all histological types of OC samples, in cancer epithelial cells, stroma cells and metastatic foci -Conflicting data on expression differences between different OC histological types - Single studies show higher expression in serous ovarian carcinoma type and chemotherapy-sensitive OC -Expression independent from disease stage, tumor size and treatment effects - Expression dependent from OC tendency to recur and metastasis -The relationship between expression in cancer epithelial cells and prognosis is contradictory. It is observed: a) Worse prognosis of patients with higher MMP-2 expression or b) No relationship between expression and prognosis of patients -The relationship between expression in stroma cells and prognosis is contradictory. It is observed: a) Shorter or b) Longer survival time of patients with higher MMP-2 expression	[14–16,139,141–148,152]
	Research in body fluids -Serum levels lowers in OC patients than in healthy women -Serum concentrations independent from OC stage -No differences in serum concentrations between OC patients and women with benign lesions -Plasma concentrations independent from patient prognosis -Higher urine levels in OC patients with normal CA-125 blood levels	[152,155,160]
MMP-9	**Research in tissues** -Expression was found in: all histological types of OC samples, in cancer epithelial cells, stroma cells and metastatic foci -Expression in physiological ovarian tissue is low or undetectable -Conflicting data on expression differences between different OC histological types - Single study shows higher expression in high-grade serous OC -Higher expression in OC than in benign lesions -Higher expression in OC patients with present metastatic foci than in patients without metastatic foci -Expression dependent on OC stage (higher expression in more advanced stage), and number of vasculogenic-like networks -The relationship between expression in OC tissue and prognosis is contradictory. It is observed: a) Shorter or b) Longer survival time of patients with higher MMP-9 expression	[14,139–148]
	Research in body fluids -No correlation between serum concentrations and OC histological types -Serum and plasma concentrations higher in OC patients compared to healthy women and those with benign lesions -Serum concentrations higher in more advanced stage OC and in patients insensitive to chemotherapy and with ascites or metastatic foci - Plasma concentrations independent of patients prognosis -Decline in serum concentrations after surgery - Highest sensitivity values in assays with CA-125 in plasma - Higher urine levels in OC patients with normal CA-125 blood levels	[14,152,156–158,160]

(*Continued*)

Table 2 (Continued).

Gelatinases		
MMP	**Results**	**References**
Collagenases		
MMP	**Results**	**References**
MMP-1	**Research in tissues** -Activity was found in physiological ovarian tissue -Expression was found in OC samples -Higher expression in OC than in benign lesions	[16,161,163–166]
	Research in body fluids -Low activity in ovarian cyst fluid -There was no difference between activity in the fluids from malignant and benign cysts	[164]
MMP-8	**Research in tissues** -Expression in physiological ovarian tissue and benign lesions has not been studied -Expression was found in OC samples -Expression dependent on OC stage (higher expression in more advanced stage - Higher expression was associated with worse prognosis -Higher expression was associated with higher MMP-9 expression	[16,164,165]
	Research in body fluids -Higher activity in malignant cyst fluids compared to benign cyst fluids	[164]
MMP-13	**Research in tissues** -Not expressed in physiological ovarian tissue -Expression in begin lesions has not been studied -Expression was found in OC samples -Expression independent from disease stage or whether cancer occupied one or two ovaries -Higher expression was associated with worse prognosis of patients	[16,164–166]
	Research in body fluids -Low activity in ovarian cyst fluid -Higher expression in peritoneal fluid was associated with worse prognosis of patients	[164,167]
MMP-18	**Research in tissues** -Expression was found in physiological ovarian tissue -Expression in OC tissue and benign lesions was not studied	[162]
Stromelysins		
MMP	**Results**	**References**
MMP-3	**Research in tissues** -Expression was found in physiological ovarian tissue and in OC samples -Expression dependent on OC stage (higher expression in more advanced stage) -Expression independent from patients prognosis	[16,166,170–173]
	Research in body fluids -Serum concentrations higher in OC patients compared to women with benign lesions -Serum concentrations dependent on OC stage (higher concentration in more advanced stage) -High serum levels were associated with shorter progression-free time and worse overall survival	[174]

(*Continued*)

Table 2 (Continued).

Gelatinases		
MMP	**Results**	**References**
MMP-10	**Research in tissues** -Not expressed in physiological ovarian tissue -Expression was found in OC samples -High expression associated with better overall survival of patients in stage III and IV in accordance with FIGO	[16,166,171,172]
MMP-11	**Research in tissues** -Expression in physiological ovarian tissue has not been studied -Expression was found in OC samples -Higher expression was associated with higher expression of MMP-2 and MMP-13 -Expression dependent on OC stage (higher expression in more advanced stage) -Expression independent from patients prognosis	[16,166,171–173]
Matrilysins		
MMP	**Results**	**References**
MMP-7	**Research in tissues** -Low expression in physiological ovarian tissue -Expression was found in: OC tissues, stroma cells, metastatic foci and in the mucin of mucinous ovarian carcinoma -Conflicting data on expression differences between OC and begin lesions. It is observed: a) Higher expression in serous OC compared to benign lesions or b) Higher expression in benign lesions compared to serous OC -Conflicting data on the relationship between expression and prognosis. It is observed: a) Better prognosis in patients with high expression of MMP-7 or b) Expression independent from patients prognosis -Low expression associated with advanced stage, high histological grade OC and large primary residual tumor	[16,117,143,144,166,175–177,179]
	Research in body fluids -Serum and plasma concentrations higher in OC patients compared to healthy women and begin lesions -No relationship between serum levels and tumor stage and grade, presence of metastasis or ascites -Positive correlation between serum concentrations and primary tumor size -Decrease in serum concentrations after surgery and chemotherapy -Parallel to CA-125 and HE4 values of diagnostic parameters (sensitivity, specificity, negative and positive predictive values) after determination from plasma	[155,179–181]
MMP-26	**Research in tissues** -High or low expression depending on the structure of the ovary -Expression was found in OC samples -Differences in expression between OC and benign lesions have not been studied -Expression dependent on OC stage (higher expression in stage III and IV compared to stage I) -No relationship between expression and prognosis of patients with OC	[16,155,166,178,179]

(*Continued*)

Table 2 (Continued).

Gelatinases		
MMP	**Results**	**References**
Membrane-type MMPs		
MMP	**Results**	**References**
MMP-14	**Tissue expression** -Conflicting data on expression in physiological ovarian tissue. It is observed: a) Expression in physiological ovarian tissue or b) No expression in physiological ovarian tissue -Expression was found in: OC samples, in cancer epithelial cells and in stroma cells -Simultaneous expression in cancer epithelial cells and stroma associated with ascites and lymph node involvement -High expression in epithelial cells associated with the development of distant metastatic foci -High expression in OC tissue was associated with low CA-125 expression -Conflicting data on expression differences between OC and begin lesions. It is observed: a) higher expression in OC compared to benign lesions or b) No expression in benign lesions -Relationship between expression in cancer epithelial cells and stroma and prognosis different or contradictory. It is observed: a) High expression simultaneously in epithelium and stroma was associated with low disease-related survival rates, b) High expression only in epithelial cells was associated with the lowest disease-related survival rates, c) Moderate expression in cancer epithelial cells with concomitant low expression in stroma was associated with the best prognosis of patients and d) No correlation between expression and prognosis of patients.	[13,16,142,144,166,173,183–187,189]
	Research in body fluids -Serum concentrations higher in OC patients compared to healthy women and begin lesions	[190]
MMP-15	**Tissue expression** -Conflicting data on expression in physiological ovarian tissue. It is observed: a) Expression in physiological ovarian tissue or b) No expression in physiological ovarian tissue -Expression was found in OC samples -Expression independent from patients prognosis	[16,166,183–185]
MMP-16	**Tissue expression** -Conflicting data on expression in physiological ovarian tissue. It is observed: a) Expression in physiological ovarian tissue or b) No expression in physiological ovarian tissue -Expression was found in OC samples -Expression dependent on OC stage (higher expression in more advanced stage) -Expression independent from patients prognosis	[16,166,183–185,188]
MMP-17	**Tissue expression** -Conflicting data on expression in physiological ovarian tissue. It is observed: a) Expression in physiological ovarian tissue or b) No expression in physiological ovarian tissue -Expression was found in OC samples -Expression independent from OC stage -Expression independent from patients prognosis	[16,166,183–185]
MMP-24	**Tissue expression** -Conflicting data on expression in physiological ovarian tissue. It is observed: a) Expression in physiological ovarian tissue or b) No expression in physiological ovarian tissue -Expression was found in OC samples -Expression independent from OC stage -Expression independent from patients prognosis	[16,166,183–185]

(*Continued*)

Table 2 (Continued).

Gelatinases		
MMP	**Results**	**References**
MMP-25	**Tissue expression** -Conflicting data on expression in physiological ovarian tissue. It is observed: a) Expression in physiological ovarian tissue or b) No expression in physiological ovarian tissue -Expression was found in OC samples -Expression dependent on OC stage (higher expression in more advanced stage) -Higher expression was associated with longer overall survival	[16,166,183–185]
Other types of MMPs		
MMP	**Results**	**References**
MMP-12	**Tissue expression** -Not expressed in physiological ovarian tissue -Expression was found in serous and endometrioid OC -Expression independent from OC stage -High expression in OC samples was associated with better overall survival (stage III or IV patients)	[16,166]
MMP-19	**Tissue expression** -Expression in physiological ovarian tissue has not been studied -Expression was found in serous and endometrioid OC -Expression independent from OC stage -The relationship between expression in OC samples and prognosis is contradictory. It is observed: a) High expression associated with poor overall survival or b) Expression independent from patients prognosis	[16,166]
MMP-20	**Tissue expression** -Expression in physiological ovarian tissue has not been studied -Expression was found in serous and endometrioid OC -Expression independent from OC stage -The relationship between expression in OC samples and prognosis is contradictory. It is observed: a) High expression associated with poor overall survival or b) Expression independent from patients prognosis	[16,166]
MMP-21	**Tissue expression** -Expression in physiological ovarian tissue has not been studied -Expression was found in serous and endometrioid OC -Expression independent from patients prognosis	[16,166]

MMP-8, MMP-9, and MMP-14) has been associated with a more unfavorable disease course. Conversely, the potentially protective properties of some MMPs, including MMP-7 and MMP-25, have been demonstrated. In addition to tissue expression, some studies have preliminarily established the utility of MMPs as markers in peripheral blood, urine, and other body fluids. However, as with tissue expression assays, these data are incomplete and often conflicting. Nevertheless, according to initial studies, individual enzymes from the MMP family such as MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, and MMP-14 may be suitable for early diagnosis, monitoring, and assessing prognosis of patients with ovarian cancer. A clear determination of the diagnostic utility of these enzymes requires further research. A summary of the diagnostic potential of individual MMPs is presented in Figure 4.
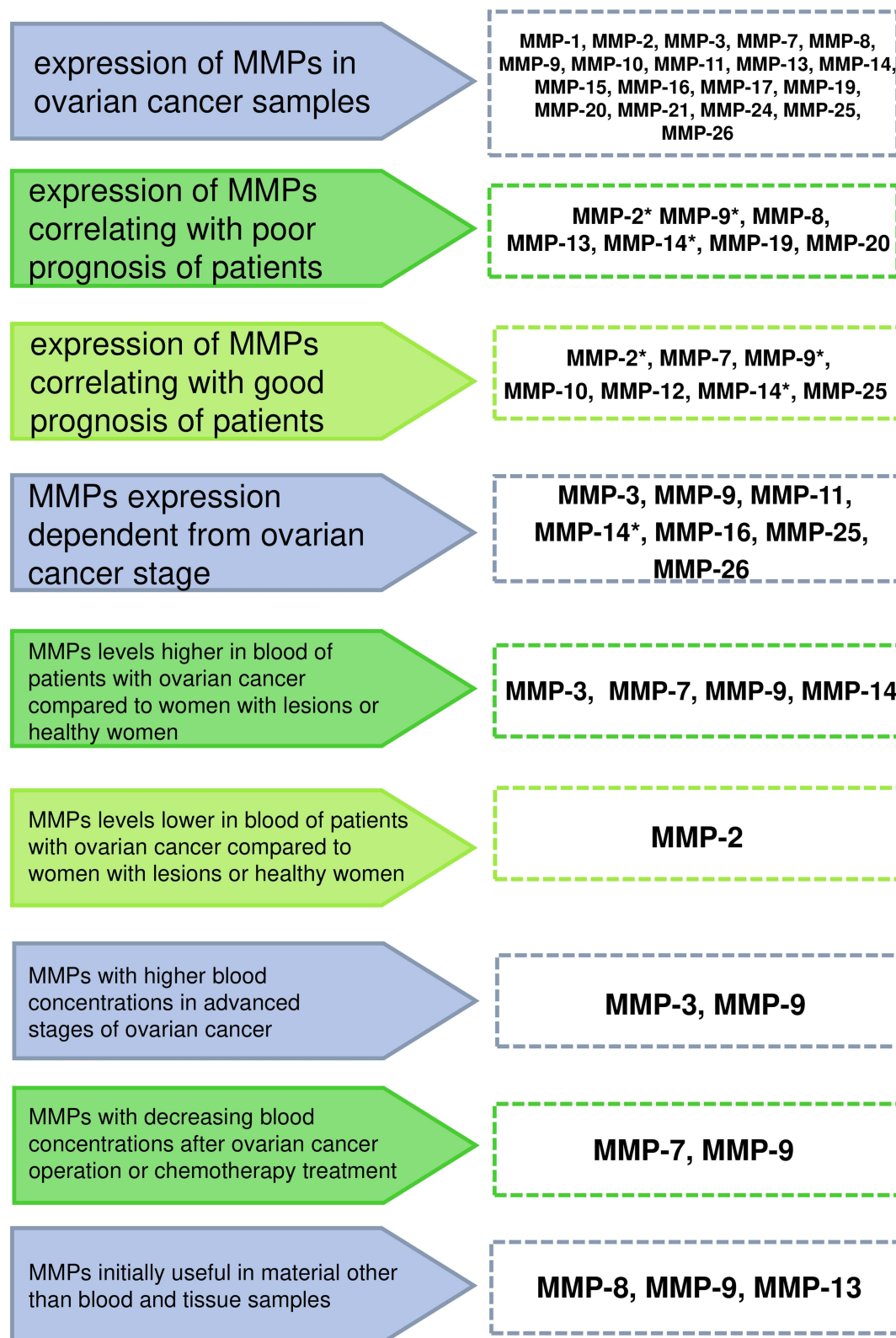
Funding

Figure 4 Diagnostic potential of individual MMPs in ovarian cancer patients. *Conflicting data about respective MMPs were shown in separate studies.
Abbreviations: MMP-1, Metalloproteinase-1; MMP-2, Metalloproteinase-2; MMP-3, Metalloproteinase-3; MMP-7, Metalloproteinase-7; MMP-8, Metalloproteinase-8; MMP-9, Metalloproteinase-9; MMP-10, Metalloproteinase-10; MMP-11, Metalloproteinase-11; MMP-12, Metalloproteinase-12; MMP-13, Metalloproteinase-13; MMP-14, Metalloproteinase-14; MMP-15, Metalloproteinase-15; MMP-16, Metalloproteinase-16; MMP-17, Metalloproteinase-17; MMP-18, Metalloproteinase-18; MMP-19, Metalloproteinase-19; MMP-20, Metalloproteinase-20; MMP-21, Metalloproteinase-21; MMP-24, Metalloproteinase-24; MMP-25, Metalloproteinase-25; MMP-26, Metalloproteinase-26; MMPs, Matrix metalloproteinases.

Disclosure

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