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REVIEW



Update value and clinical application of MUC16 (cancer antigen 125)

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ABSTRACT

Introduction: The largest transmembrane mucin, mucin 16 (MUC16), contains abundant glycosylation sites on the molecular surface, allowing it to participate in various molecular pathways. When cells lose polarity and become cancerous, MUC16 is overexpressed, and more of the extracellular region (cancer antigen [CA]125) is released into serum and possibly, promote the development of diseases. Thus, MUC16 plays an indispensable role in clinical research and application.

Areas covered: This review summarizes the update proposed role of MUC16 in carcinogenesis and metastasis. Most importantly, we prospect its potential value in targeted therapy after screening 1226 articles published within the last 10 years from PubMed. Two reviewers screened each record and each report retrieved independently. We have summarized the progress of MUC16/CA125 in basic research and clinical application, and predicted its possible future development directions.

Expert opinion: As an important noninvasive co-factor in the diagnosis of gynecological diseases, MUC16 has been used for a long time, especially in the diagnosis and treatment of ovarian cancer. The overexpression of MUC16 plays a very obvious role in regulating inflammatory response, supporting immune suppression, and promoting the proliferation, division, and metastasis of cancer cells. In the next 20 years, there will be a luxuriant clinical application of MUC16 as a target for immune monitoring and immunotherapy.

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1. Introduction

1.1. Composition and structure of mucin 16 (MUC16)

Mucin 16 (MUC16) is a transmembrane mucin with an average molecular weight of 3–5 million Da. It is expressed on the surface of various epithelial cells, and the extracellular fraction released into the serum is referred to as cancer antigen (CA) 125 [1,2]. CA125 is considered a glycoprotein complex with an abundant epitope map released into the serum via phosphorylation of MUC16. MUC16 contains a C-terminal and N-terminal domain, which sandwich an extended, highly glycosylated, abundant tandem repeat domain [3]. MUC16 contains many potential sites in the tandem repeat domain and the N-terminal domain for O-linked and N-linked glycosylation, such as serine and threonine residues [4]. The C-terminal domain is the smallest part of MUC16 and comprises an extracellular part, a transmembrane region, and a cytoplasmic tail. Though the C-terminal domain only has 284 amino acids, it plays an indispensable role in MUC16. Phosphorylation of the cytoplasmic tail domain may cause the extracellular portion to break away from MUC16 [5] (Figure 1). There is ongoing research to improve our understanding of MUC16 cleavage.

2. Generation and function

2.1. Generation

Transmembrane mucin is a highly glycosylated protein. This high glycosylation level not only shelters the extracellular domain from endogenous and exogenous injuries but also contributes to forming a protective barrier [6]. MUC16 is expressed on many epithelia, such as the ocular and tracheal surface [7], where it contributes to the mucosa's protection, lubrication, and maintenance [8]. Morgado et al. found that nuclear factor kappa B (NF- κ B) is important for stimulating MUC16 since MUC16 contains a binding site for NF- κ B [9]. Furthermore, Das et al. found that the Golgi/post-Golgi compartments' acidic environment may cause MUC16 cleavage [10]. It is currently accepted that elevated CA125 levels follow the loss of polarity of normal cells and MUC16 overexpression during carcinogenesis. MUC16 is subsequently cleaved close to the transmembrane domain, potentially causing an increase in CA125 levels [6]. Ascites in patients with ovarian cancer (OC) can also stimulate the expression of MUC16 in mesenchymal cells through a protein kinase B (AKT)-dependent pathway, thus forming a positive-feedback loop [11]. As the specific location and detailed structure of CA125 remain unclear, a more detailed study of the decomposition process is needed.

Article highlights

- Latest progress in basic research and clinical aspects of MUC16/CA125.
- The role of MUC16/CA125 in the development of tumors.
- Application of MUC16/CA125 in benign and malignant diseases.
- Research progress on MUC16/CA125 as a new target for immunoimaging and immunotherapy.
- The limitations and issues that need to be addressed in current research on MUC16/CA125.

2.2. Function

In addition to protection and lubrication, MUC16 also contributes to carcinogenesis, inflammatory responses, and metastasis [12]. In resting, normal, and polarized cells, the expression of MUC16 is intricately controlled and restricted to the free surface of epithelia. When cell polarity is lost during carcinogenesis, MUC16 is overexpressed and redistributed all over cell surfaces, enhancing its interaction with multiple molecules [8,12] (Figure 2).

Mucin 16 (MUC16) is overexpressed during the proliferation and metastasis of multiple tumors. In a study of MUC16 in breast and lung cancer (LC), researchers found that MUC16 plays a role in the Janus kinase 2 (JAK2)-activator of transcription 3 (STAT3) pathway and can promote the phosphorylation of c-Jun [13]. Moreover, MUC16 promotes the proliferation of breast cancer (BC) cells by promoting a rapid G2/M transition and inhibiting apoptosis via tumor necrosis factor-related apoptosis-inducing ligand-mediated extrinsic apoptotic signaling [14,15]. In addition, the

C-terminal of MUC16 May be related to the secretion of tumor-derived interleukin 6 (IL-6), which promotes tumor-associated Treg activation in the JAK2/STAT3 pathway [16]. When IL-6 R binds to IL-6, the activation of the NF- κ B signaling pathway can be triggered, and NF- κ B binds to the MUC16 promoter resulting in the overexpression of MUC16, forming a positive-feedback pathway (Figure 3(a)).

The uncontrolled proliferation of cancer cells demands a large amount of energy, and MUC16 is also involved in the abnormal metabolism of cancer cells. Wang et al. found that MUC16 can promote glycogen synthesis and enable tumor cells to produce more energy for proliferation by regulating glucose transporter 1, ultimately controlling glucose uptake of epithelial ovarian cancer cells [17]. Additionally, MUC16 can activate the AMP-activated protein kinase pathway and induce the glycolysis and proliferation of gall bladder carcinoma cells by promoting aldolase C stability and disrupting the ability of aldolase C to detect glucose deficiency [18]. What's more, epidermal growth factor (EGF) receptor, an ErbB-type receptor, can be activated by binding EGF-like domains on abnormal glycosylated MUC16; thus, its downstream effectors, phosphoinositide 3-kinase/AKT/glycogen synthase kinase 3 beta (GSK3 β), can be activated. Subsequently, cellular processes, especially glycogen and protein synthesis, are also affected [19,20] (Figure 3(b)).

MUC16 mediates metastasis of cancer cells to the peritoneum through interaction with mesothelin (MSLN). Studies have demonstrated that CA125 combined with mesothelin can enhance cancer cell adherence and promote metastasis via elevation of metalloproteinase (MMP)-7 levels and promotion of p38 mitogen-activated protein kinase

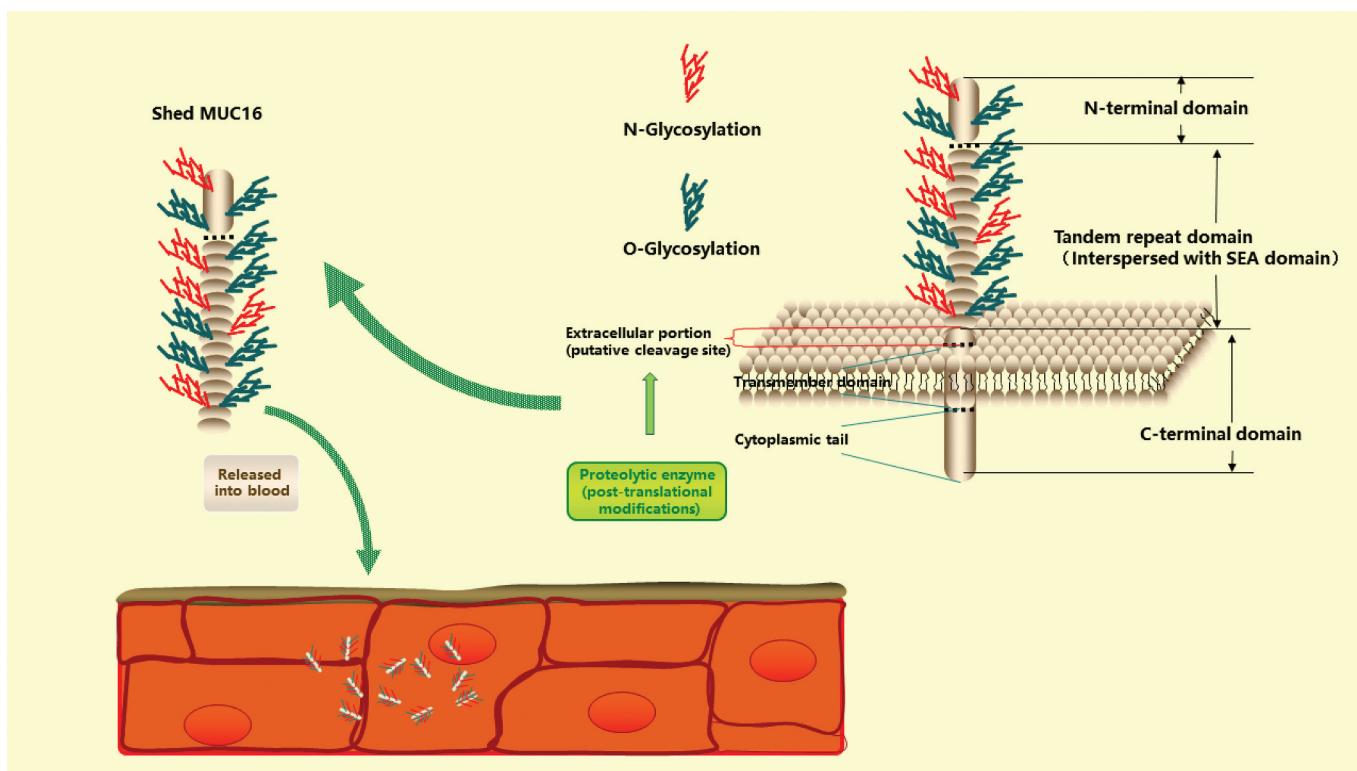


Figure 1. The structure of MUC16, as currently accepted.

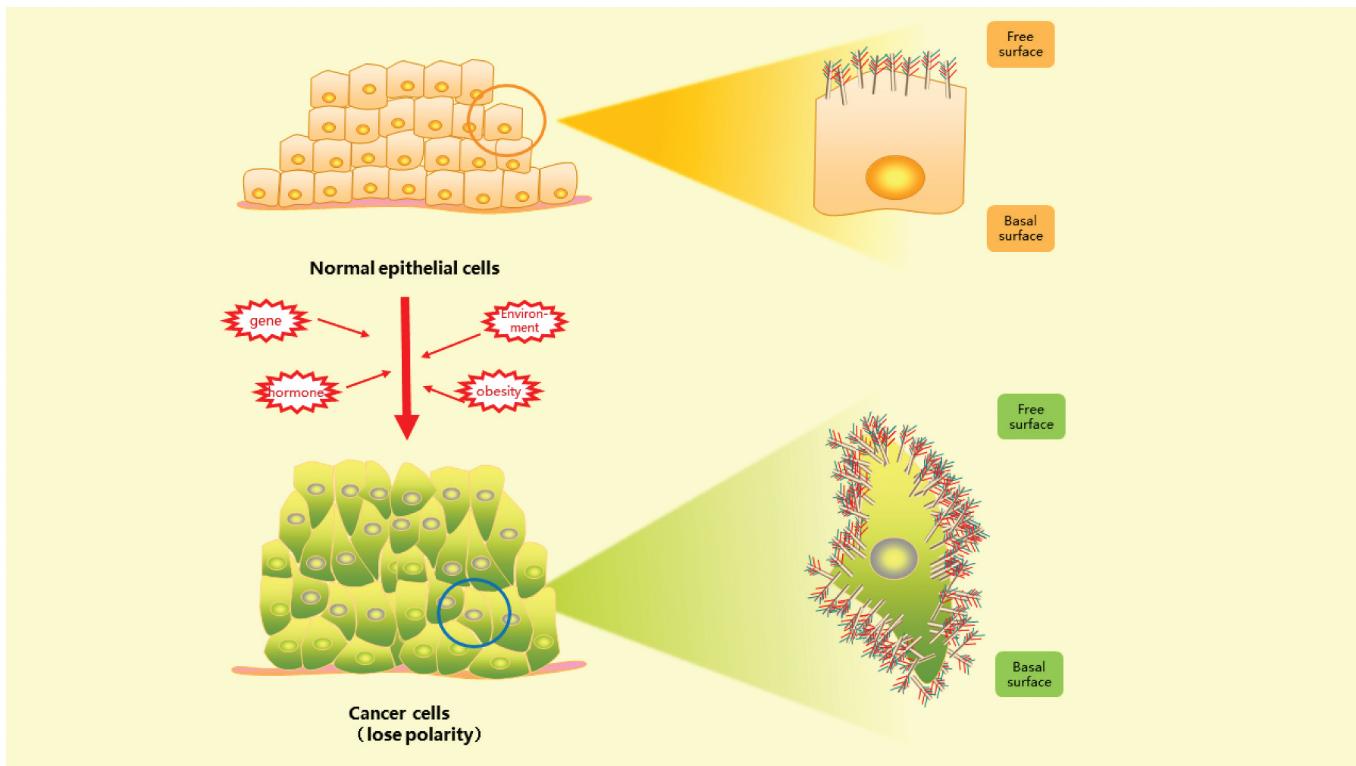


Figure 2. Abnormal expression of MUC16 in cancer cells without polarization.

phosphorylation [21–23]. Huo et al. suggested that this mechanism may be related to the serum- and glucocorticoid-inducible kinase 3/forkhead box O3 pathway [24]. In addition, MUC16 can bind to selectins (e.g. E/L-selectin) to promote pancreatic cancer (PC) cell metastasis [25]. Ovarian cancer cells disseminate in the peritoneal cavity by forming three-dimensional multicellular aggregates after shedding from the primary tumor tissue. Giannakouros et al. found that MUC16 can promote this process by inhibiting β -catenin degradation [26]. Additionally, MUC16 can activate the Wnt signaling pathway and promote tumorigenesis and metastasis by interacting with β -catenin [27]. Suppressing the MUC16 gene in cancer cells reportedly halted the metastasis of tumor cells associated with reduced MMP-2 activation [28] (Figure 3(c)).

Tumor development is associated with immune suppression and evasion; studies have noted that MUC16 can inhibit immune responses. Gubbels et al. found that MUC16 can help ovarian cancer cells evade immune recognition by inhibiting the formation of immune synapses [29]. Meanwhile, MUC16 can engage sialic acid-binding Ig-like lectin-9, an immune cell suppressor, blocking tumor-immune cell interactions in humans [30] and inhibiting the cytolytic functions of immune cells [31]. Following MUC16 overexpression, increased CA125 will directly bind to IgG1 and suppress its combination with the CD16a Fc γ receptor on the cell surface to impact antibody-dependent cell-mediated cytotoxicity of natural killer cells. In addition, this mechanism blocks complement-dependent cytotoxicity via suppression of C1q-antibody binding [32] (Figure 3(d)).

3. Clinical application of CA125 in malignant disease

3.1. Ovarian cancer

CA125 is mostly used for ovarian cancer screening, which has been applied clinically since 1981 [2]. Although CA125 is also expressed in normal ovarian cells, the serum level in patients with OC is usually elevated, often by several hundred-fold. The threshold of clinical application is currently 35 U/mL; patients with levels exceeding this threshold should be closely observed.

Regarding early detection, a recent study found that among all patients with OC, the time from test to diagnosis for females with elevated CA125 levels was shorter than that for females with normal levels [33], indicating that abnormal CA125 levels have predictive value in early diagnosis of OC. Among epithelial OCs, CA125 is most frequently elevated in serous carcinomas [34]. In addition, a study found that high levels of two CA125 glycoforms (CA125-STn and CA125-MGL) in the serum may indicate an increased tumor burden post-surgery [35]. A recent study also reported a high (69%) sensitivity of CA125 in diagnosing endometrioid ovarian carcinomas [36]. CA125 can also be used to support the diagnosis of other histological OCs, including mucinous ovarian carcinoma [37], clear cell ovarian carcinoma [38,39], and transitional cell tumors [40].

No clear relationship has been observed between the survival and tissue CA125 expression of patients with early-stage OC. However, among patients with late-stage OC, patients with normal CA125 levels have significantly shorter OC-specific survival than that of patients with elevated CA125

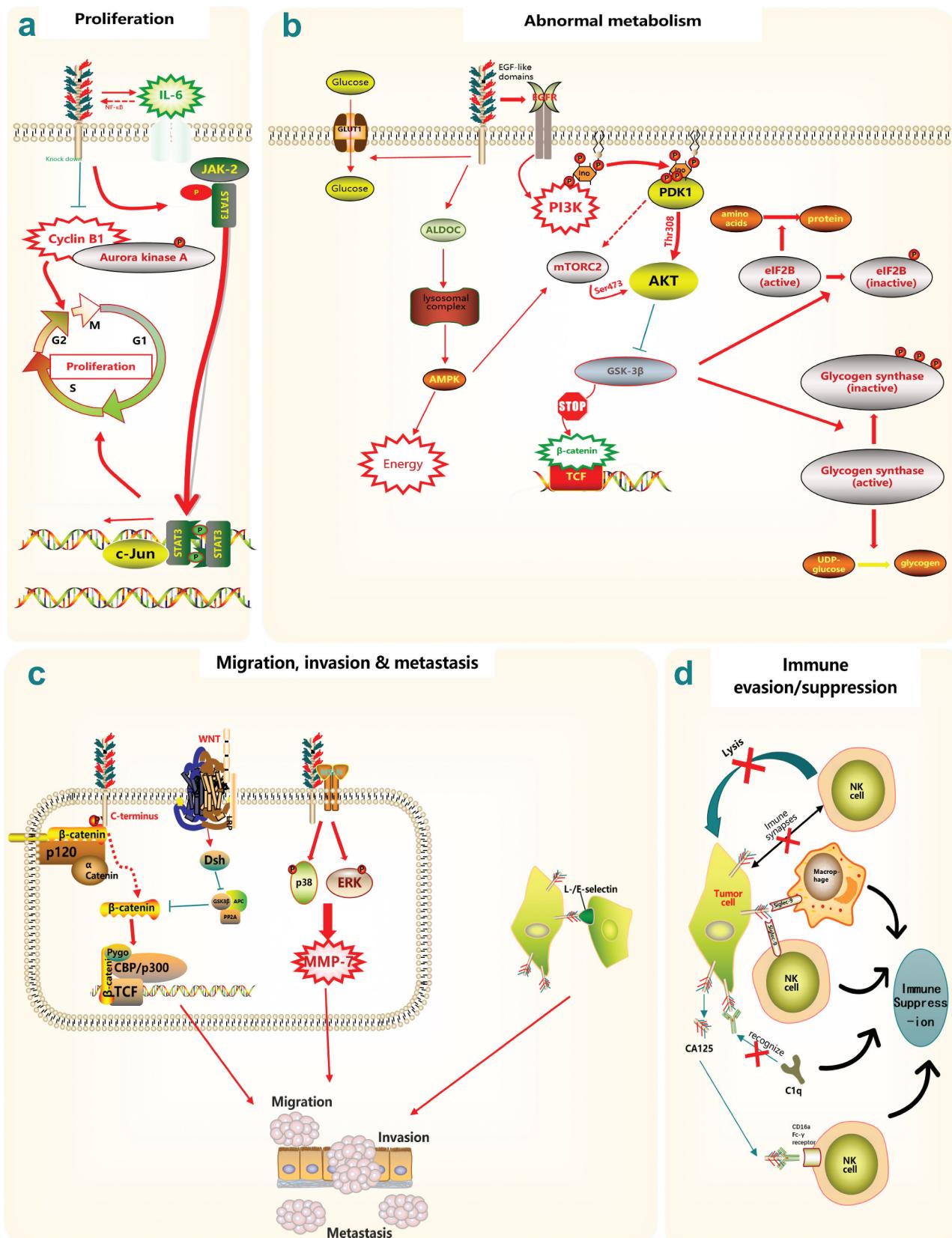


Figure 3. Proposed functions of MUC16 in cancer cells. (a) proliferation of cancer cells following interaction with Janus kinase 2 (JAK2), mediating activator of transcription 3 (STAT3) and c-Jun phosphorylation. G2/M arrest occurs in MUC16-silenced conditions; (b) abnormal metabolism of cancer cells through the regulation of glucose transporter 1 (GLUT1) and aldolase C, affecting glycogen and protein synthesis by activating epidermal growth factor receptor (EGFR) and its downstream effectors phosphoinositide 3-kinase/protein kinase B/glycogen synthase kinase 3 beta (PI3K/AKT/GSK3 β); (c) Promotion of cancer cell migration, invasion, and metastasis through interaction with mesothelin (MSLN), E-/L-selectin, and inhibition of β-catenin degradation; (d) immune evasion/suppression of cancer cells by blockade of tumor-immune cell interactions and inhibition of antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and the cytolytic functions of immune cells.



levels [41]. Moreover, among patients with elevated CA125, relatively lower CA125 levels predict early stages and improve prognosis [42]. May et al. reported that if the CA125 value decreased by more than seven times after surgery, it may indicate better survival for patients with high-grade serous OC [43]. In recent studies of CA125 and chemotherapy, a low serum CA125 level and fast normalizing rate were associated with improved clinical outcomes of chemotherapy and long progression-free survival [44,45]. Unfortunately, the further increase of CA125 levels after operation in patients with elevated CA125 levels during OC progression indicates that the disease is relapsing; however, in patients with no evident initial increase in CA125 levels, it is unclear whether CA125 elevation indicates disease recurrence.

Early-stage OC cannot be distinguished from benign diseases using CA125 alone; therefore, an effective method to overcome this and enhance accuracy is to measure CA125 together with the human epididymal protein 4 (HE4) and comparatively analyze the results [46]. The HE4 (also known as WFC2) is an elevated glycoprotein among most patients with OC, especially in endometrioid OC, and weakly expressed in benign diseases, such as endometrioma with high CA125 levels [47]. Therefore, it has become an effective index for distinguishing OC from other conditions. However, unlike CA125, HE4 levels can be affected by multiple confounding factors, including smoking [48] and contraceptive use [49]. Therefore, these two indicators should be applied experiencedly at the same time. Moreover, the combination of CA125 and HE4 can boost the diagnostic efficiency of epithelial OC, including serous and endometrioid ovarian carcinomas [46].

3.2. Endometrial carcinoma (EC)

Presently, the diagnosis of EC requires careful consideration of ultrasound, magnetic resonance imaging, and tumor markers. When used individually, none of these methods perform satisfactorily. Many studies have found that CA125 levels were associated with histological and clinical parameters, including lymphovascular invasion [50], lymph node metastases, and adnexal involvement [51]. A multicenter prospective cohort study found that elevated CA125 levels in patients with low-risk EC may represent a poor outcome and should be considered as seriously as high-risk EC to receive adjuvant treatment [52]. However, selecting an appropriate reference cutoff value is still a major factor influencing the clinical application of CA125. Some researchers have proposed that adjusting the CA125 cutoff according to patient age is more helpful for clinical decision-making; they indicated that the suitable CA125 cutoff was 105 U/mL for premenopausal patients with EC, not 35 U/mL, which is used for postmenopausal females [53].

To overcome the low sensitivity of CA125, researchers suggest that combining CA125 with other serum markers can more accurately diagnose EC. Various markers can be combined with CA125, including HE4 [54,55], CA724 [56], CA19-9, and MSLN [57]. Among these applications, HE4 and MSLN appeared most frequently. Studies investigating the combined use of HE4 and CA125 have confirmed their predictive role in the prognosis and recurrence of EC, especially for grade 3

endometrioid carcinoma and special types of EC [58]. When HE4 and CA125 are combined with body mass index, the sensitivity and specificity of EC diagnosis are further increased; this may be explained by EC being an obesity-related disease [59]. As a protein normally produced by mesothelial cells, MSLN can interact well with the N-linked glycans on CA125. Most patients with EC and elevated CA125 have accompanying elevated MSLN levels [60].

3.3. Lung cancer

In studies investigating the auxiliary diagnosis of LC, CA125 is important in the serum, pleural effusion [61], and bronchoalveolar lavage fluid. In patients with late-stage LC, CA125 positivity is relatively high [62]. Compared with using CA125 alone, diagnostic efficiency can be improved by combining CA125 with other biomarkers [63–65]. Zang et al. optimized a model to help detect LC and demonstrate higher efficacy than that offered by protein markers alone via statistical analysis [66]. In the 1990s, researchers started to notice the prognostic value of serum CA125 for survival and tumor relapse in LC, especially in non-small-cell lung cancer [67,68]. Kanwal et al. reported that high levels of MUC16 May increase resistance to cisplatin and enhance migration and invasion of LC cells [69]. This may be because MUC16 can promote growth and migration, enhancing resistance to drugs such as cisplatin and gemcitabine in LC cells via the JAK2/STAT3/GR downstream signaling pathways [15]. *ERO1L* (a potentially related gene that affects protein secretion) promotes IL-6/sIL-6 R signaling and increases the expression of MUC16/CA125 in a positive-feedback mode, thereby impacting the prognosis of LC [70]. Indeed, joint detection is more meaningful than single detection [71]. In addition, the detection of serum CA125 concentration alone or in combination with other biomarkers [72] can predict LC metastasis, including bone [73], eye [74,75], brain [76], and liver metastasis. However, this does not necessarily mean that the prognosis is good or there is a low risk of metastasis. It is noteworthy that the serum CA125 concentration in male patients with LC is not statistically significantly higher than that in female patients, even though the female ovary, uterus, or other organs may be affected [77].

3.4. Breast cancer

The main role of serum CA125 in preoperative evaluation is in early diagnosis [78] and predicting metastasis [79] of BC. Determination of CA125 serum values in combination with human epidermal growth factor receptor 2 [80], MSLN [81], carcinoembryonic antigen (CEA) [82] and CA15-3 [83,84] can increase the sensitivity of detecting metastases and predicting prognosis. However, CA15-3 and CEA seem to be more meaningful compared to CA125 [85].

In addition, the degree of elevation of serum tumor markers may reflect the overall tumor burden in the body, both clinically and sub-clinically. When the tumor burden is low, serum tumor markers are more suitable for postoperative monitoring rather than for early diagnosis and metastasis screening. Fang et al. found significant differences in preoperative CA125 serum levels among different molecular

subtypes; elevated CA125 and CA15–3 levels always indicated a large tumor diameter (>5 cm) and increased lymph node metastases [86]. Furthermore, as a major and common symptom, nipple discharge in patients with BC is abnormal, with higher levels of CA125, CEA, and CA153 than those in healthy controls, particularly in intraductal papilloma [87].

This year, studies on triple-negative breast cancer (TNBC) confirmed that MUC16 is the promoter of TNBC lung metastasis and works through the HuR/cMyc axis [88]. These latest discoveries may provide direction in the treatment (like targeted liposomes with MUC16) and prevention of development and lung metastasis of TNBC [89].

3.5. Cervical cancer (CC)

Tumor markers used for the screening and evaluation of CC include CA125, CEA, squamous cell carcinoma antigen, serum fragments of cytokeratin [90], and long non-coding RNA colon cancer-associated transcript 2 [91]. Research has demonstrated the best diagnostic performance for CEA [92,93]. Current studies on the application of CA125 in CC state that among patients with adverse pathologic CC, high serum CA125 levels at diagnosis and monitoring after operation indicated poor prognosis as well as increased severity, para-uterine invasion, and lymph node metastases [94,95].

3.6. Pancreatic cancer

MUC16/CA125 plays an important role in carcinogenesis [96], metastasis [97], resectability [98], and drug-resistant properties of PC [99]. Research on the immunological aspects of PC has shown that neoantigen quality, rather than quantity, can better reflect the tumor progression and immune monitoring process [100]. CA19–9 is the only guideline-recommended tumor marker for pancreatic ductal adenocarcinoma (PDAC); however, its application is limited in early-stage patients or those with biliary obstruction compared with that of CA125 [101–103]. Furthermore, CEA and HE4 [104] are valuable markers for monitoring and predicting PDAC [105,106]. In Lewis-negative patients, CEA and CA125 are most effective when used for differential diagnosis [107]. Therefore, detecting multiple rather than single biomarkers may represent another breakthrough for patients with PDAC [108,109]. Studies have also investigated the mechanism of action of MUC16 and its use in targeted therapy. The serum content of MUC16 in patients with PC is usually higher than that in healthy individuals, possibly due to the KRAS/c-Myc axis being a promoter for MUC16 upregulation [110]. MUC16 is an aberrantly O-glycosylated glycoprotein that is detected in tumors, which can interact with ErbB receptors to activate AKT and GSK3β signaling pathways and promote metastasis and glycolysis (Figure 3(b)) [111]. The interaction with selectin and MSLN of MUC16 plays an important role in the metastasis of PC. Moreover, MUC16 can promote the activation of tumor-secreted IL-6 in the JAK2/STAT3 signaling pathway, enhancing the expression of Foxp3 and tumor-associated Treg enrichment [112]. In the intricate process of cell signal communication, some scholars found that PI3K/AKT and ERK/MAPK pathway can also be activated in the interaction

between MUC16 and Integrin. FAK phosphorylation may be a very critical step [113,114]. Therefore, mucin-targeted therapies gained a hotspot in the current research scenario. MUC16 is a feasible target for intraoperative imaging and as a therapeutic agent in PC [115].

4. Clinical application of CA125 in benign disease

4.1. Endometriosis (EM)

Elevated serum CA125 can also be observed in patients with EM; therefore, it can be applied in early diagnosis and predicting prognosis as an index of EM [116]. According to a bivariate hierarchical model summarizing accuracy data from 14 studies (total of 2920 participants) using CA125 ≥ 30 U/mL, the specificity of CA125 was 93% (95% CI 89–95%), and the sensitivity was 52% (95% CI 38–66%). In addition, with the increase in tumor volume, CA125 was significantly more sensitive for the diagnosis, from 24% (95% CI 19–32%) to 63% (95% CI 47–77%) ($P = 0.001$) [117]. EM is also affected by the menstrual cycle [118], which indicates that CA125 can be affected by the occurrence and progress of EM. Oliveira et al. also found the level of CA125 to be significantly increased during the menstrual and mid-menstrual periods in patients with deep-infiltrating EM. This finding may help to shorten the interval between the first symptoms and a definitive diagnosis [119]. Due to the high rate of EM recurrence, researchers focus on early diagnosis and prognosis monitoring. Similar to OC, the increase and further increase of CA125 (>35 U/mL) levels may be associated with the development and recurrence of EM [120].

4.2. Adenomyosis (AM)

AM is a common gynecological disease manifested by the displacement of endometrial glands and stroma into the myometrium. AM frequently occurs with hysteromyoma, endometrial polyps, and endometriosis. Similar to EM, the main clinical features of adenomyosis are infertility, dysmenorrhea, and pelvic pain. Currently, transvaginal sonography is the most common diagnostic technique used in outpatient clinics [121]. Although the application of CA125 is still limited in the diagnosis of AM, its role in differential diagnosis has been confirmed. After collecting 2911 consecutive samples from patients between January 2000 and December 2005, Kil et al. found that serum CA125 testing was the least invasive, most cost-effective, simplest, and fastest method for screening AM with or without EM and the differential diagnosis of AM and myoma [122]. There are also case reports of patients with severe adenomyosis and unexpectedly high CA125 levels exceeding 900 IU/mL [123,124]. In addition, high serum CA125 levels may be related to a poor disease prognosis [125,126]. Nevertheless, due to the low specificity of CA125 in benign diseases, its clinical application in AM remains limited.

5. MUC16 as a target

So far, studies in the light of MUC16 as a target have emerged in an endless stream. These mainly include two parts, targeted detection and targeted therapy. Researchers have identified two types of anti-MUC16 monoclonal antibodies: those



targeting the N-terminal tandem repeat epitopes and those targeting the cleaved cytoplasmic tail. However, the sensitivity and specificity of these antibodies remain controversial. The most frequently used antibody in the clinic targets is cleaved CA125 in serum. However, the levels detected are significantly lower than the total amount of expressed MUC16. Clinical studies are combined with other disciplines, such as electrochemistry, to improve detection efficiency [127–129].

MUC16 has been used in radioimmunosintigraphy and radioimmunotherapy to detect residual disease. For instance, AR9.6-IRDye800 can be used for the image-guided resection of PC as a fluorescent MUC16-targeted antibody probe developed by Olson et al. [130]. In contrast, MUC16 is more widely used in targeted immunotherapy, including immunotherapy of CA125, anti-idiotype vaccine, MUC16 antibody-drug conjugates, MUC16 ectodomain chimeric antigen receptor T cells, and targeting MUC16-MSLN interactions [8]. Recently, multiple studies have investigated antibodies targeting MUC16 [131,132]. REGN4018, a human bispecific antibody first reported by Crawford et al., was found to activate T cells and kill MUC16-expressing tumor cells in OC with favorable tolerability [133]. In addition, AR9.6 can provide an antibody for image guiding in immunoPET and is a highly promising theragnostic agent due to its excellent *in vivo* tumor-targeting properties [134].

6. Conclusion

MUC16, the largest member of the transmembrane mucin family, comprises an amino-terminal, carboxyl-terminal, and intermediate tandem repeats. The abundant amino acid reserves in the structure endow it with a variety of biochemical reaction sites, which enable it to exert important roles in many signal pathways. As a highly glycosylated transmembrane mucin, MUC16 is normally distributed on the surface of epithelial cells and contributes to lubricating and protecting the mucosa. However, with loss of polarity during epithelial cell carcinogenesis, MUC16 (CA125) is overexpressed and plays a more obvious role in regulating inflammatory response, supporting immune suppression, and promoting the proliferation, division, and metastasis of cancer cells. This is the basic theory of disease surveillance based on serum CA125 values. Although the detection efficiency of CA125 is relatively limited in the early stage of disease development due to the relatively light cancer burden, CA125 has important reference value in the preoperative diagnosis and postoperative monitoring of middle and advanced cancers. In the early diagnosis of two benign diseases affected by the menstrual cycle, EM and AM, CA125 is often found in auxiliary examinations by clinicians. Due to the high recurrence rate of these two diseases, routine CA125 screening has also become an important indicator for monitoring recurrence. If serum CA125 is greater than 35 U/mL or increased to more than twice after surgery, it is likely to predict disease recurrence.

Recently, increasing studies have focused on MUC16 as a target for radioimmunoimaging and radioimmunotherapy. It is used in combination with other disciplines and is also gaining interest. A high-precision MUC16-targeted antibody can accurately guide procedures and elucidate the size of residual lesions after surgery. In addition, an anti-MUC16 antibody has the potential as a cancer therapy.

7. Expert opinion

As an important noninvasive co-factor in the diagnosis of gynecological diseases, MIUC16 has been used for a long time, especially in the diagnosis and treatment of OC. Abnormal elevation of serum CA125 during early physical examination or post-operative screening, alerts health care workers to notice the newborn or recurrent disease. CA125 possesses an extracellular peptide epitope of MUC16. Studies have shown that it plays an important role in the screening of tumors and predictions of prognosis and recurrence. However, due to false positives and false negatives in CA125 detection, its clinical application remains limited. To overcome this, CA125 can be combined with other relevant tumor markers, such as HE4, to help the early detection of OC and promote differentiation between OC and other benign diseases. Abnormal increases in CA125 can also be used as an early diagnostic standard for EC; however, the premise is to select an appropriate reference value. The traditional cutoff value for postmenopausal females is 35 U/mL, whereas the cutoff for premenopausal females is recommended to be increased to 105 U/mL. Similarly, CA125 can also be detected in the serum and pleural effusions of some patients with LC. Overexpression of MUC16 (CA125) can enhance the resistance of LC cells to chemotherapy drugs and promote their growth and migration. However, the application of CA125 in breast and CC is very limited. It is mainly used for auxiliary diagnosis and prognosis when the tumor load is high, that is, during the middle and late stages of disease development. Another important application of CA125 is in PC. Clinicians can use CA125 levels to help determine the tumorigenicity, metastasis, resectability, and drug resistance of PC cells. In addition, immunography and immunotherapy targeting MUC16 also play a significant role in controlling disease progression. Before operations, the areas with rich MUC16 expression shown by immunography can be marked with emphasis. The MUC16 expression measured by this method is more accurate than that in serum, which is very conducive to the comprehensive surgical removal of lesions. After surgery completion, close monitoring of MUC16 reexpression in the lesion by immunography, if conditions permit, is also of great value for predicting disease recurrence.

However, it has to be admitted that the main reason for the restriction of development lies in its low specificity and incomplete mechanism research. We cannot determine the main role of MUC16 in the occurrence and development of diseases. At present, we know that MUC16 can be seen in many pathways that promote the differentiation and development of cancer cells. Is the increased expression of MUC16 due to cancerous cells or is the abnormal expression of MUC16 a factor that promotes cancer? This is an urgent question that needs to be answered.

The development of medicine is a slow process with a high error rate. We believe that with further study of the specific structure of MUC16/CA125 and its production process in the body, the important role it plays in the complex process of the occurrence and development of diseases will be further revealed. In terms of clinical application, immunotherapy is currently an important measure to solve the high recurrence rate of cancer. Many articles on the immunogenicity of MUC16 have indicated that it plays an important role in immunity. In the next 5 to 10 years, MUC16 will definitely play a surprising role in immunotherapy. Specifically, the outstanding contribution of immunotherapy

represented by anti-MUC16 antibodies in future disease control will further highlight the clinical application value of MUC16.

Abbreviations

MUC16	mucin 16
CA	cancer antigen
NF-κB	nuclear factor kappa B
AKT	protein kinase B
JAK2	Janus kinase 2
STAT3	activator of transcription 3
IL-6	interleukin 6
GLUT1	glucose transporter 1
EGF	epidermal growth factor
MSLN	mesothelin
MMP	metalloproteinase
OC	ovarian cancer
CA125-MGL	recombinant human macrophage galactose-type lectin
CA125-STn	Sialyl-Thomsen-nouveau
HE4	human epididymal protein 4
EC	endometrial carcinoma
LC	lung cancer
BC	breast cancer
CEA	carcinoembryonic antigen
CC	cervical cancer
PC	pancreatic cancer
PDAC	pancreatic ductal adenocarcinoma
GSK3β	glycogen synthase kinase-3 beta
EM	endometriosis
AM	adenomyosis

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Author contributions

YA Song took part in the conception of this review, screened each record and each report retrieved, drafted the manuscript, and prepared the figures. M Yuan screened each record and each report retrieved, and revised the article. GY Wang revised the article and performed the final approval of the version to be submitted.

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References

- Mitić N, Kosanović M, Milutinović B, et al. Nano-sized CA125 antigen glycocomouflage: mucin - extracellular vesicles alliance to watch? *Arch Biochem Biophys.* 2018;653:113–120. doi: [10.1016/j.abb.2018.06.017](https://doi.org/10.1016/j.abb.2018.06.017)
- Yin BW, Lloyd KO. Molecular cloning of the ca125 ovarian cancer antigen. Identification as a new mucin, muc16. *J Biol Chem.* 2001;276:27371–27375. doi: [10.1074/jbc.M103554200](https://doi.org/10.1074/jbc.M103554200)
- O'Brien TJ, Beard JB, Underwood LJ, et al. The CA125 gene: an extracellular superstructure dominated by repeat sequences. *Tumour Biol.* 2001;22:348–346. doi: [10.1159/000050638](https://doi.org/10.1159/000050638)
- Lloyd KO, Yin BW, Kudryashov V. Isolation and characterization of ovarian cancer antigen CA 125 using a new monoclonal antibody (VK-8): identification as a mucin-type molecule. *Int J Cancer.* 1997;71:842–850. doi: [10.1002/\(SICI\)1097-0215\(19970529\)71:5<842::AID-IJC24>3.0.CO;2-8](https://doi.org/10.1002/(SICI)1097-0215(19970529)71:5<842::AID-IJC24>3.0.CO;2-8)
- Fendrick JL, Staley KA, Gee MK, et al. Characterization of CA 125 synthesized by the human epithelial amnion WISH cell line. *Tumour Biol.* 1993;14(5):310–318. doi: [10.1159/000217844](https://doi.org/10.1159/000217844)
- van Putten JPM, Strijbis K. Transmembrane mucins: Signaling receptors at the intersection of inflammation and cancer. *J Innate Immun.* 2017;9:281–299. doi: [10.1159/000453594](https://doi.org/10.1159/000453594)
- Paulsen F, Jäger K, Worlitzsch D, et al. Regulation of MUC16 by inflammatory mediators in ocular surface epithelial cell lines. *Ann Anat.* 2008;190(1):59–70. doi: [10.1016/j.aanat.2007.05.001](https://doi.org/10.1016/j.aanat.2007.05.001)
- Aithal A, Rauth S, Kshirsagar P, et al. MUC16 as a novel target for cancer therapy. *Expert Opin Ther Targets.* 2018;22(8):675–686. doi: [10.1080/14728222.2018.1498845](https://doi.org/10.1080/14728222.2018.1498845)
- Morgado M, Sutton MN, Simmons M, et al. Tumor necrosis factor-α and interferon-γ stimulate MUC16 (CA125) expression in breast, endometrial and ovarian cancers through NFκB. *Oncotarget.* 2016;7(12):14871–14884. doi: [10.1863/oncotarget.7652](https://doi.org/10.1863/oncotarget.7652)
- Das S, Majhi PD, Al-Mugotir MH, et al. Membrane proximal ectodomain cleavage of MUC16 occurs in the acidifying Golgi/post-Golgi compartments. *Sci Rep.* 2015;5(1):9759. doi: [10.1038/srep09759](https://doi.org/10.1038/srep09759)
- Matte I, Garde-Granger P, Bessette P, et al. Ascites from ovarian cancer patients stimulates MUC16 mucin expression and secretion in human peritoneal mesothelial cells through an Akt-dependent pathway. *BMC Cancer.* 2019;19(1):406. doi: [10.1186/s12885-019-5611-7](https://doi.org/10.1186/s12885-019-5611-7)
- Haridas D, Chakraborty S, Ponnusamy MP, et al. Pathobiological implications of MUC16 expression in pancreatic cancer. *PLoS One.* 2011;6(10):e26839. doi: [10.1371/journal.pone.0026839](https://doi.org/10.1371/journal.pone.0026839)
- Das S, Rachagani S, Torres-Gonzalez MP, et al. Carboxyl-terminal domain of MUC16 imparts tumorigenic and metastatic functions through nuclear translocation of JAK2 to pancreatic cancer cells. *Oncotarget.* 2015;6(8):5772–5787. doi: [10.1863/oncotarget.3308](https://doi.org/10.1863/oncotarget.3308)
- Lakshmanan I, Ponnusamy MP, Das S, et al. MUC16 induced rapid G2/M transition via interactions with JAK2 for increased proliferation and anti-apoptosis in breast cancer cells. *Oncogene.* 2012;31(7):805–817. doi: [10.1038/onc.2011.297](https://doi.org/10.1038/onc.2011.297)
- Lakshmanan I, Salfty S, Seshacharyulu P, et al. MUC16 regulates TSPYL5 for lung cancer cell growth and chemoresistance by suppressing p53. *Clin Cancer Res.* 2017;23(14):3906–3917. doi: [10.1158/1078-0432.CCR-16-2530](https://doi.org/10.1158/1078-0432.CCR-16-2530)
- Shimizu A, Hirono S, Tani M, et al. Coexpression of MUC16 and mesothelin is related to the invasion process in pancreatic ductal adenocarcinoma. *Cancer Sci.* 2012;103(4):739–746. doi: [10.1111/j.1349-7006.2012.02214.x](https://doi.org/10.1111/j.1349-7006.2012.02214.x)
- Wang F, Zhang Q, Zhang H, et al. MUC16 promotes EOC proliferation by regulating GLUT1 expression. *J Cell Mol Med.* 2021;25(6):3031–3040. doi: [10.1111/jcmm.16345](https://doi.org/10.1111/jcmm.16345)
- Fan K, Wang J, Sun W, et al. MUC16 C-terminal binding with ALDOC disrupts the ability of ALDOC to sense glucose and promotes

- gallbladder carcinoma growth. *Exp Cell Res.* **2020**;394(1):112118. doi: [10.1016/j.yexcr.2020.112118](https://doi.org/10.1016/j.yexcr.2020.112118)
19. Frame S, Cohen P. GSK3 takes centre stage more than 20 years after its discovery. *Biochem J.* **2001**;359(Pt 1):1–16. doi: [10.1042/bj3590001](https://doi.org/10.1042/bj3590001)
 20. Thomas D, Sagar S, Liu X, et al. Isoforms of MUC16 activate oncogenic signaling through EGF receptors to enhance the progression of pancreatic cancer. *Mol Ther.* **2021**;29(4):1557–1571. doi: [10.1016/j.ymthe.2020.12.029](https://doi.org/10.1016/j.ymthe.2020.12.029)
 21. Gubbels JA, Belisle J, Onda M, et al. Mesothelin-MUC16 binding is a high affinity, N-glycan dependent interaction that facilitates peritoneal metastasis of ovarian tumors. *Mol Cancer.* **2006**;5(1):50. doi: [10.1186/1476-4598-5-50](https://doi.org/10.1186/1476-4598-5-50)
 22. Chen SH, Hung WC, Wang P, et al. Mesothelin binding to CA125/MUC16 promotes pancreatic cancer cell motility and invasion via MMP-7 activation. *Sci Rep.* **2013**;3(1):1870. doi: [10.1038/srep01870](https://doi.org/10.1038/srep01870)
 23. Sasaki A, Akita K, Ito F, et al. Difference in mesothelin-binding ability of serum CA125 between patients with endometriosis and epithelial ovarian cancer. *Int J Cancer.* **2015**;136(8):1985–1990. doi: [10.1002/ijc.29185](https://doi.org/10.1002/ijc.29185)
 24. Huo Q, Xu C, Shao Y, et al. Free CA125 promotes ovarian cancer cell migration and tumor metastasis by binding mesothelin to reduce DKK1 expression and activate the SGK3/FOXO3 pathway. *Int J Biol Sci.* **2021**;17(2):574–588. doi: [10.7150/ijbs.52097](https://doi.org/10.7150/ijbs.52097)
 25. Chen SH, Dallas MR, Balzer EM, et al. Mucin 16 is a functional selectin ligand on pancreatic cancer cells. *FASEB J.* **2012**;26(3):1349–1359. doi: [10.1096/fj.11-195669](https://doi.org/10.1096/fj.11-195669)
 26. Giannakouros P, Comamala M, Matte I, et al. MUC16 mucin (CA125) regulates the formation of multicellular aggregates by altering β-catenin signaling. *Am J Cancer Res.* **2014**;5:219–230.
 27. Liu Q, Cheng Z, Luo L, et al. C-terminus of MUC16 activates Wnt signaling pathway through its interaction with β-catenin to promote tumorigenesis and metastasis. *Oncotarget.* **2016**;7(24):36800–36813. doi: [10.18632/oncotarget.9191](https://doi.org/10.18632/oncotarget.9191)
 28. Reinartz S, Failer S, Schuell T, et al. CA125 (MUC16) gene silencing suppresses growth properties of ovarian and breast cancer cells. *Eur J Cancer.* **2012**;48(10):1558–1569. doi: [10.1016/j.ejca.2011.07.004](https://doi.org/10.1016/j.ejca.2011.07.004)
 29. Gubbels JA, Felder M, Horibata S, et al. MUC16 provides immune protection by inhibiting synapse formation between NK and ovarian tumor cells. *Mol Cancer.* **2010**;9(1):11. doi: [10.1186/1476-4598-9-11](https://doi.org/10.1186/1476-4598-9-11)
 30. Belisle JA, Horibata S, Jennifer GA, et al. Identification of Siglec-9 as the receptor for MUC16 on human NK cells, B cells, and monocytes. *Mol Cancer.* **2010**;9(1):118. doi: [10.1186/1476-4598-9-118](https://doi.org/10.1186/1476-4598-9-118)
 31. Thériault C, Pinard M, Comamala M, et al. MUC16 (CA125) regulates epithelial ovarian cancer cell growth, tumorigenesis and metastasis. *Gynecol Oncol.* **2011**;121(3):434–443. doi: [10.1016/j.ygyno.2011.02.020](https://doi.org/10.1016/j.ygyno.2011.02.020)
 32. Kline JB, Kennedy RP, Albone E, et al. Tumor antigen CA125 suppresses antibody-dependent cellular cytotoxicity (ADCC) via direct antibody binding and suppressed Fc-γ receptor engagement. *Oncotarget.* **2017**;8(32):52045–52060. doi: [10.18632/oncotarget.19090](https://doi.org/10.18632/oncotarget.19090)
 33. Funston G, Ta Mounce L, Price S, et al. CA125 test result, test-to-diagnosis interval, and stage in ovarian cancer at diagnosis: a retrospective cohort study using electronic health records. *Br J Gen Pract.* **2021**;71:e465–472. doi: [10.3399/BJGP.2020.0859](https://doi.org/10.3399/BJGP.2020.0859)
 34. Söletermos G, Duffy MJ, Othman Abu Hassan S, et al. Clinical use of cancer biomarkers in epithelial ovarian cancer: updated guidelines from the European group on tumor markers. *Int J Gynecol Cancer.* **2016**;26(1):43–51. doi: [10.1097/IGC.0000000000000586](https://doi.org/10.1097/IGC.0000000000000586)
 35. Salminen L, Nadeem N, Jain S, et al. A longitudinal analysis of CA125 glycoforms in the monitoring and follow up of high grade serous ovarian cancer. *Gynecol Oncol.* **2020**;156(3):689–694. doi: [10.1016/j.ygyno.2019.12.025](https://doi.org/10.1016/j.ygyno.2019.12.025)
 36. Lawicki S, Będkowska GE, Gacuta-Szumarska E, et al. The plasma concentration of VEGF, HE4 and CA125 as a new biomarkers panel in different stages and sub-types of epithelial ovarian tumors. *J Ovarian Res.* **2013**;6(1):45. doi: [10.1186/1757-2215-6-45](https://doi.org/10.1186/1757-2215-6-45)
 37. Choi JH, Sohn GS, Chay DB, et al. Preoperative serum levels of cancer antigen 125 and carcinoembryonic antigen ratio can improve differentiation between mucinous ovarian carcinoma and other epithelial ovarian carcinomas. *Obstet Gynecol Sci.* **2018**;61(3):344–351. doi: [10.5468/ogs.2018.61.3.344](https://doi.org/10.5468/ogs.2018.61.3.344)
 38. Del Carmen MG, Birrer M, Schorge JO. Clear cell carcinoma of the ovary: a review of the literature. *Gynecol Oncol.* **2012**;126:481–490. doi: [10.1016/j.ygyno.2012.04.021](https://doi.org/10.1016/j.ygyno.2012.04.021)
 39. Li M, Tan J, Zhang Y, et al. Assessing CT imaging features combined with CEA and CA125 levels to identify endometriosis-associated ovarian cancer. *Abdom Radiol.* **2021**;46(6):2367–2375. doi: [10.1007/s00261-020-02571-x](https://doi.org/10.1007/s00261-020-02571-x)
 40. Nasioudis D, Sisti G, Holcomb K, et al. Malignant Brenner tumors of the ovary: a population-based analysis. *Gynecol Oncol.* **2016**;142(1):44–49. doi: [10.1016/j.ygyno.2016.04.538](https://doi.org/10.1016/j.ygyno.2016.04.538)
 41. Høgdall EV, Christensen L, Kjaer SK, et al. CA125 expression pattern, prognosis and correlation with serum CA125 in ovarian tumor patients. From the Danish “MALOVA” ovarian cancer study. *Gynecol Oncol.* **2007**;104:508–515. doi: [10.1016/j.ygyno.2006.09.028](https://doi.org/10.1016/j.ygyno.2006.09.028)
 42. Zhang M, Cheng S, Jin Y, et al. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. *Biochim Biophys Acta Rev Cancer.* **2021**;1875(2):188503. doi: [10.1016/j.bbcan.2021.188503](https://doi.org/10.1016/j.bbcan.2021.188503)
 43. May T, Stewart JM, Bernardini MQ, et al. The prognostic value of perioperative, pre-systemic therapy CA125 levels in patients with high-grade serous ovarian cancer. *Int J Gynaecol Obstet.* **2018**;140(2):247–252. doi: [10.1002/ijgo.12376](https://doi.org/10.1002/ijgo.12376)
 44. Bachmann R, Brucker S, Stäbler A, et al. [Corrigendum] prognostic relevance of high pretreatment CA125 levels in primary serous ovarian cancer. *Mol Clin Oncol.* **2021**;14(4):8. doi: [10.3892/mco.2021.2247](https://doi.org/10.3892/mco.2021.2247)
 45. Zhang D, Jiang YX, Luo SJ, et al. Serum CA125 levels predict outcome of interval debulking surgery after neoadjuvant chemotherapy in patients with advanced ovarian cancer. *Clin Chim Acta.* **2018**;484:32–35. doi: [10.1016/j.cca.2018.04.030](https://doi.org/10.1016/j.cca.2018.04.030)
 46. Dochez V, Caillion H, Vauzel E, et al. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res.* **2019**;12(1):28. doi: [10.1186/s13048-019-0503-7](https://doi.org/10.1186/s13048-019-0503-7)
 47. Drapkin R, von Horsten HH, Lin Y, et al. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. *Cancer Res.* **2005**;65(6):2162–2169. doi: [10.1158/0008-5472.CAN-04-3924](https://doi.org/10.1158/0008-5472.CAN-04-3924)
 48. Fortner RT, Vitanis AF, Schock H, et al. Correlates of circulating ovarian cancer early detection markers and their contribution to discrimination of early detection models: results from the EPIC cohort. *J Ovarian Res.* **2017**;10(1):20. doi: [10.1186/s13048-017-0315-6](https://doi.org/10.1186/s13048-017-0315-6)
 49. Ferraro S, Schiumarini D, Panteghini M. Human epididymis protein 4: factors of variation. *Clin Chim Acta.* **2015**;438:171–177. doi: [10.1016/j.cca.2014.08.020](https://doi.org/10.1016/j.cca.2014.08.020)
 50. Kim HS, Park CY, Lee J-M, et al. Evaluation of serum CA-125 levels for preoperative counseling in endometrioid endometrial cancer: a multi-center study. *Gynecol Oncol.* **2010**;118(3):283–288. doi: [10.1016/j.ygyno.2010.04.018](https://doi.org/10.1016/j.ygyno.2010.04.018)
 51. Jiang T, Huang L, Zhang S. Preoperative serum CA125: a useful marker for surgical management of endometrial cancer. *BMC Cancer.* **2015**;15(1):396. doi: [10.1186/s12885-015-1260-7](https://doi.org/10.1186/s12885-015-1260-7)
 52. Reijnen C, Visser NC, Kasijs JC, et al. Improved preoperative risk stratification with CA-125 in low-grade endometrial cancer: a multicenter prospective cohort study. *J Gynecol Oncol.* **2019**;30:e70. doi: [10.3802/jgo.2019.30.e70](https://doi.org/10.3802/jgo.2019.30.e70)
 53. Chao A, Tang YH, Lai CH, et al. Potential of an age-stratified CA125 cut-off value to improve the prognostic classification of patients with endometrial cancer. *Gynecol Oncol.* **2013**;129(3):500–504. doi: [10.1016/j.ygyno.2013.02.032](https://doi.org/10.1016/j.ygyno.2013.02.032)
 54. Wang Y, Han C, Teng F, et al. Predictive value of serum HE4 and CA125 concentrations for lymphatic metastasis of endometrial cancer. *Int J Gynaecol Obstet.* **2017**;136(1):58–63. doi: [10.1002/ijgo.12010](https://doi.org/10.1002/ijgo.12010)
 55. Antonsen SL, Høgdall E, Christensen IJ, et al. HE4 and CA125 levels in the preoperative assessment of endometrial cancer patients: a prospective multicenter study (ENDOMET). *Acta Obstet Gynecol Scand.* **2013**;92(11):1313–1322. doi: [10.1111/aogs.12235](https://doi.org/10.1111/aogs.12235)
 56. Bian J, Sun X, Li B, et al. Clinical significance of serum HE4, CA125, CA724, and CA19-9 in patients with endometrial cancer. *Technol Cancer Res Treat.* **2017**;16(4):435–439. doi: [10.1177/1533034616666644](https://doi.org/10.1177/1533034616666644)

57. Kakimoto S, Miyamoto M, Einama T, et al. Significance of mesothelin and CA125 expression in endometrial carcinoma: a retrospective analysis. *Diagn Pathol*. 2021;16(1):28. doi: [10.1186/s13000-021-01093-4](https://doi.org/10.1186/s13000-021-01093-4)
58. Quan Q, Liao Q, Yin W, et al. Serum HE4 and CA125 combined to predict and monitor recurrence of type II endometrial carcinoma. *Sci Rep*. 2021;11(1):21694. doi: [10.1038/s41598-021-01263-w](https://doi.org/10.1038/s41598-021-01263-w)
59. Krifcic T, Osredkar J, Smrkolić Š, et al. Novel algorithm including CA-125, HE4 and body mass index in the diagnosis of endometrial cancer. *Gynecol Oncol*. 2017;147(1):126–132. doi: [10.1016/j.ygyno.2017.07.130](https://doi.org/10.1016/j.ygyno.2017.07.130)
60. Kakimoto S, Miyamoto M, Einama T, et al. Co-expression of mesothelin and CA125 is associated with the poor prognosis of endometrial serous carcinoma and mixed carcinomas including serous carcinoma. *Pathol Oncol Res*. 2020;26(4):2299–2306. doi: [10.1007/s12253-020-00823-1](https://doi.org/10.1007/s12253-020-00823-1)
61. Zhang H, Li C, Hu F, et al. Auxiliary diagnostic value of tumor biomarkers in pleural fluid for lung cancer-associated malignant pleural effusion. *Respir Res*. 2020;21(1):284. doi: [10.1186/s12931-020-01557-z](https://doi.org/10.1186/s12931-020-01557-z)
62. Nakamura H, Nishimura T. History, molecular features, and clinical importance of conventional serum biomarkers in lung cancer. *Surg Today*. 2017;47(9):1037–1059. doi: [10.1007/s00595-017-1477-y](https://doi.org/10.1007/s00595-017-1477-y)
63. Yang Q, Zhang P, Wu R, et al. Identifying the best marker combination in CEA, CA125, CY211, NSE, and SCC for lung cancer screening by combining ROC curve and logistic regression analyses: Is it feasible? *Dis Markers*. 2018;2018:2082840. doi: [10.1155/2018/2082840](https://doi.org/10.1155/2018/2082840)
64. Chen Z, Wang Y, Fang M. Analysis of tumor markers in pleural effusion and serum to verify the correlations between serum tumor markers and tumor size, TNM stage of lung adenocarcinoma. *Cancer Med*. 2020;9(4):1392–1399. doi: [10.1002/cam4.2809](https://doi.org/10.1002/cam4.2809)
65. Li Y, Tian X, Gao L, et al. Clinical significance of circulating tumor cells and tumor markers in the diagnosis of lung cancer. *Cancer Med*. 2019;8(8):3782–3792. doi: [10.1002/cam4.2286](https://doi.org/10.1002/cam4.2286)
66. Zang R, Li Y, Jin R, et al. Enhancement of diagnostic performance in lung cancers by combining CEA and CA125 with autoantibodies detection. *Oncoimmunology*. 2019;8(10):e1625689. doi: [10.1080/2162402X.2019.1625689](https://doi.org/10.1080/2162402X.2019.1625689)
67. Diez M, Torres A, Pollán M, et al. Prognostic significance of serum CA 125 antigen assay in patients with non-small cell lung cancer. *Cancer*. 1994;73:1368–1376. doi: [10.1002/1097-0142\(19940301\)73:5<1368::AID-CNCR2820730510>3.0.CO;2-O](https://doi.org/10.1002/1097-0142(19940301)73:5<1368::AID-CNCR2820730510>3.0.CO;2-O)
68. Isaksson S, Jönsson P, Monsef N, et al. CA 19-9 and CA 125 as potential predictors of disease recurrence in resectable lung adenocarcinoma. *PLoS One*. 2017;12(10):e0186284. doi: [10.1371/journal.pone.0186284](https://doi.org/10.1371/journal.pone.0186284)
69. Kanwal M, Ding XJ, Song X, Song X, et al. MUC16 overexpression induced by gene mutations promotes lung cancer cell growth and invasion. *Oncotarget*. 2018;9(15):12226–12239. doi: [10.18632/oncotarget.24203](https://doi.org/10.18632/oncotarget.24203)
70. Lei Y, Zang R, Lu Z, et al. ERO1L promotes IL6/sIL6R signaling and regulates MUC16 expression to promote CA125 secretion and the metastasis of lung cancer cells. *Cell Death Dis*. 2020;11(10):853. doi: [10.1038/s41419-020-03067-8](https://doi.org/10.1038/s41419-020-03067-8)
71. Chen XK, Gu CL, Fan JQ, et al. P-STAT3 and IL-17 in tumor tissues enhances the prognostic value of CEA and CA125 in patients with lung adenocarcinoma. *Biomed Pharmacother*. 2020;125:109871. doi: [10.1016/j.biopha.2020.109871](https://doi.org/10.1016/j.biopha.2020.109871)
72. Ren X, Zhang Y, Lyu Y, et al. Lactate dehydrogenase and serum tumor markers for predicting metastatic status in geriatric patients with lung adenocarcinoma. *Cancer Biomark*. 2019;26:139–150. doi: [10.3233/CBM-190201](https://doi.org/10.3233/CBM-190201)
73. Zhou Y, Yu QF, Peng AF, et al. The risk factors of bone metastases in patients with lung cancer. *Sci Rep*. 2017;7(1):8970. doi: [10.1038/s41598-017-09650-y](https://doi.org/10.1038/s41598-017-09650-y)
74. Li B, Yuan Q, Zou YT, et al. CA-125, CA-153, and CYFRA21-1 as clinical indicators in male lung cancer with ocular metastasis. *J Cancer*. 2020;11(10):2730–2736. doi: [10.7150/jca.36238](https://doi.org/10.7150/jca.36238)
75. Shi WQ, Liu WF, Li B, et al. Assessment of serum tumor markers for predicting ocular metastasis in lung adenocarcinoma: a retrospective study. *Dis Markers*. 2020;2020:2102158. doi: [10.1155/2020/2102158](https://doi.org/10.1155/2020/2102158)
76. Wang H, Shen L, Geng J, et al. Prognostic value of cancer antigen -125 for lung adenocarcinoma patients with brain metastasis: a random survival forest prognostic model. *Sci Rep*. 2018;8(1):5670. doi: [10.1038/s41598-018-23946-7](https://doi.org/10.1038/s41598-018-23946-7)
77. Wang CF, Peng SJ, Liu RQ, et al. The combination of CA125 and NSE is useful for predicting liver metastasis of lung cancer. *Dis Markers*. 2020;2020:8850873. doi: [10.1155/2020/8850873](https://doi.org/10.1155/2020/8850873)
78. Chen R, Jiang C, Zhu Q, et al. Combining the tumor abnormal protein test with tests for carcinoembryonic antigens, cancer antigen 15-3, and/or cancer antigen 125 significantly increased their diagnostic sensitivity for breast cancer. *Medicine*. 2020;99:e21231. doi: [10.1097/MD.0000000000001231](https://doi.org/10.1097/MD.0000000000001231)
79. Zhang J, Wei Q, Dong D, et al. The role of TPS, CA125, CA15-3 and CEA in prediction of distant metastasis of breast cancer. *Clin Chim Acta*. 2021;523:19–25. doi: [10.1016/j.cca.2021.08.027](https://doi.org/10.1016/j.cca.2021.08.027)
80. Baskić D, Ristić P, Matić S, et al. Clinical evaluation of the simultaneous determination of CA 15-3, CA 125 and sHER2 in breast cancer. *Biomarkers*. 2007;12(6):657–667. doi: [10.1080/13547500701520563](https://doi.org/10.1080/13547500701520563)
81. Einama T, Yamagishi Y, Takihata Y, et al. Co-expression of mesothelin and CA125/MUC16 is a prognostic factor for breast cancer, especially in luminal-type breast cancer patients. *Biomark Res*. 2021;9(1):78. doi: [10.1186/s40364-021-00335-3](https://doi.org/10.1186/s40364-021-00335-3)
82. Li X, Dai D, Chen B, et al. Prognostic values of preoperative serum CEA and CA125 levels and nomograms for young breast cancer patients. *Onco Targets Ther*. 2019;12: 8789–8800. doi: [10.2147/OTT.S221335](https://doi.org/10.2147/OTT.S221335)
83. Zhao W, Li X, Wang W, et al. Association of preoperative serum levels of CEA and CA15-3 with molecular subtypes of breast cancer. *Dis Markers*. 2021;2021:5529106. doi: [10.1155/2021/5529106](https://doi.org/10.1155/2021/5529106)
84. Wang W, Xu X, Tian B, et al. The diagnostic value of serum tumor markers CEA, CA19-9, CA125, CA15-3, and TPS in metastatic breast cancer. *Clin Chim Acta*. 2017;470:51–55. doi: [10.1016/j.cca.2017.04.023](https://doi.org/10.1016/j.cca.2017.04.023)
85. Li J, Liu L, Feng Z, et al. Tumor markers CA15-3, CA125, CEA and breast cancer survival by molecular subtype: a cohort study. *Breast Cancer*. 2020;27(4):621–630. doi: [10.1007/s12282-020-01058-3](https://doi.org/10.1007/s12282-020-01058-3)
86. Fang C, Cao Y, Liu X, et al. Serum CA125 is a predictive marker for breast cancer outcomes and correlates with molecular subtypes. *Oncotarget*. 2017;8(38):63963–63970. doi: [10.18632/oncotarget.19246](https://doi.org/10.18632/oncotarget.19246)
87. Zhao S, Mei Y, Wang J, et al. Different levels of CEA, CA153 and CA125 in milk and benign and malignant nipple discharge. *PLoS One*. 2016;11(6):e0157639. doi: [10.1371/journal.pone.0157639](https://doi.org/10.1371/journal.pone.0157639)
88. Chaudhary S, Appadurai MI, Maurya SK, et al. MUC16 promotes triple-negative breast cancer lung metastasis by modulating RNA-binding protein ELAVL1/HUR. *Breast Cancer Res*. 2023;25(1):25. doi: [10.1186/s13058-023-01630-7](https://doi.org/10.1186/s13058-023-01630-7)
89. Hagimori M, Kato N, Orimoto A, et al. Development of triple-negative breast cancer-targeted liposomes with MUC16 binding peptide ligand in triple-negative breast cancer cells. *J Pharm Sci*. 2023;112(6):1740–1745. doi: [10.1016/j.xphs.2023.02.025](https://doi.org/10.1016/j.xphs.2023.02.025)
90. Dasari S, Wudayagiri R, Valluru L. Cervical cancer: biomarkers for diagnosis and treatment. *Clin Chim Acta*. 2015;445:7–11. doi: [10.1016/j.cca.2015.03.005](https://doi.org/10.1016/j.cca.2015.03.005)
91. Cao X, Yao J, Jia M, et al. Serum CCAT2 as a biomarker for adjuvant diagnosis and prognostic prediction of cervical cancer. *J Ovarian Res*. 2022;15(1):20. doi: [10.1186/s13048-022-00950-0](https://doi.org/10.1186/s13048-022-00950-0)
92. Dolscheid-Pommerich RC, Keyver-Paik M, Hecking T, et al. Clinical performance of LOCIT™-based tumor marker assays for tumor markers CA 15-3, CA 125, CEA, CA 19-9 and AFP in gynecological cancers. *Tumour Biol*. 2017;39(10):1010428317730246. doi: [10.1177/1010428317730246](https://doi.org/10.1177/1010428317730246)
93. Huang G, Chen R, Lu N, et al. Combined evaluation of preoperative serum CEA and CA125 as an independent prognostic biomarker in patients with early-stage cervical adenocarcinoma. *Onco Targets Ther*. 2020;13: 5155–5164. doi: [10.2147/OTT.S250614](https://doi.org/10.2147/OTT.S250614)
94. Kim N, Park W, Cho WK, et al. Significance of serum CA125 level in surgically resected cervical adenocarcinoma with adverse features. *J Gynecol Oncol*. 2021;32(5):e72. doi: [10.3802/jgo.2021.32.e72](https://doi.org/10.3802/jgo.2021.32.e72)



95. Zhou Y, Shen L, Wang YZ, et al. The potential of ciRS-7 for predicting onset and prognosis of cervical cancer. *Neoplasma*. **2020**;67:312–322. doi: [10.4149/neo_2019_190415N334](https://doi.org/10.4149/neo_2019_190415N334)
96. Hogendorf P, Durczyński A, Skulimowski A, et al. Growth differentiation factor (GDF-15) concentration combined with CA125 levels in serum is superior to commonly used cancer biomarkers in differentiation of pancreatic mass. *Cancer Biomark.* **2018**;21:505–511. doi: [10.3233/CBM-170203](https://doi.org/10.3233/CBM-170203)
97. Liu L, Xu HX, Wang WQ, et al. Serum CA125 is a novel predictive marker for pancreatic cancer metastasis and correlates with the metastasis-associated burden. *Oncotarget*. **2016**;7(5):5943–5956. doi: [10.18632/oncotarget.6819](https://doi.org/10.18632/oncotarget.6819)
98. Luo G, Xiao Z, Long J, et al. CA125 is superior to CA19-9 in predicting the resectability of pancreatic cancer. *J Gastrointest Surg*. **2013**;17(12):2092–2098. doi: [10.1007/s11605-013-2389-9](https://doi.org/10.1007/s11605-013-2389-9)
99. Liu L, Xiang J, Chen R, et al. The clinical utility of CA125/MUC16 in pancreatic cancer: a consensus of diagnostic, prognostic and predictive updates by the Chinese study group for pancreatic cancer (CSPAC). *Int J Oncol*. **2016**;48(3):900–907. doi: [10.3892/ijo.2015.3316](https://doi.org/10.3892/ijo.2015.3316)
100. Luo G, Liu C, Guo M, et al. Potential biomarkers in Lewis negative patients with pancreatic cancer. *Ann Surg*. **2017**;265(4):800–805. doi: [10.1097/SLA.0000000000001741](https://doi.org/10.1097/SLA.0000000000001741)
101. Diab HMH, Smith HG, Jensen KK, et al. The current role of blood-based biomarkers in surgical decision-making in patients with localised pancreatic cancer: a systematic review. *Eur J Cancer*. **2021**;154:73–81. doi: [10.1016/j.ejca.2021.05.033](https://doi.org/10.1016/j.ejca.2021.05.033)
102. Chang JC, Kundranda M. Novel diagnostic and predictive biomarkers in pancreatic adenocarcinoma. *Int J Mol Sci*. **2017**;18(3):667. doi: [10.3390/ijms18030667](https://doi.org/10.3390/ijms18030667)
103. Swords DS, Firpo MA, Scaife CL, et al. Biomarkers in pancreatic adenocarcinoma: current perspectives. *Onco Targets Ther*. **2016**;9:7459–7467. doi: [10.2147/OTT.S100510](https://doi.org/10.2147/OTT.S100510)
104. Huang T, Jiang SW, Qin L, et al. Expression and diagnostic value of HE4 in pancreatic adenocarcinoma. *Int J Mol Sci*. **2015**;16(2):2956–2970. doi: [10.3390/ijms16022956](https://doi.org/10.3390/ijms16022956)
105. Huang Z, Li Z, Jiang M, et al. Homogeneous multiplex immunoassay for one-step pancreatic cancer biomarker evaluation. *Anal Chem*. **2020**;92(24):16105–16112. doi: [10.1021/acs.analchem.0c03780](https://doi.org/10.1021/acs.analchem.0c03780)
106. Xu HX, Li S, Wu CT, et al. Postoperative serum CA19-9, CEA and CA125 predicts the response to adjuvant chemoradiotherapy following radical resection in pancreatic adenocarcinoma. *Pancreatology*. **2018**;18(6):671–677. doi: [10.1016/j.pan.2018.05.479](https://doi.org/10.1016/j.pan.2018.05.479)
107. Coppin L, Benomar K, Corfietti F, et al. CA-125, but not galectin-3, complements CA 19-9 for discriminating ductal adenocarcinoma versus non-malignant pancreatic diseases. *Pancreatology*. **2016**;16(1):115–120. doi: [10.1016/j.pan.2015.10.008](https://doi.org/10.1016/j.pan.2015.10.008)
108. Hogendorf P, Skulimowski A, Durczyński A, et al. A panel of CA19-9, Ca125, and Ca15-3 as the enhanced test for the differential diagnosis of the pancreatic lesion. *Dis Markers*. **2017**;2017:8629712. doi: [10.1155/2017/8629712](https://doi.org/10.1155/2017/8629712)
109. Ge L, Pan B, Song F, et al. Comparing the diagnostic accuracy of five common tumour biomarkers and CA19-9 for pancreatic cancer: a protocol for a network meta-analysis of diagnostic test accuracy. *BMJ Open*. **2017**;7(12):e018175. doi: [10.1136/bmjopen-2017-018175](https://doi.org/10.1136/bmjopen-2017-018175)
110. Liang C, Qin Y, Zhang B, et al. Oncogenic KRAS targets MUC16/CA125 in pancreatic ductal adenocarcinoma. *Mol Cancer Res*. **2017**;15(2):201–212. doi: [10.1158/1541-7786.MCR-16-0296](https://doi.org/10.1158/1541-7786.MCR-16-0296)
111. Shukla SK, Gunda V, Abrego J, et al. MUC16-mediated activation of mTOR and c-Myc reprograms pancreatic cancer metabolism. *Oncotarget*. **2015**;6(22):19118–19131. doi: [10.18632/oncotarget.4078](https://doi.org/10.18632/oncotarget.4078)
112. Fan K, Yang C, Fan Z, et al. MUC16 C terminal-induced secretion of tumor-derived IL-6 contributes to tumor-associated Treg enrichment in pancreatic cancer. *Cancer Lett*. **2018**;418:167–175. doi: [10.1016/j.canlet.2018.01.017](https://doi.org/10.1016/j.canlet.2018.01.017)
113. Rajesh C, Sagar S, Rathinavel AK, et al. Truncated O-Glycan-bearing MUC16 enhances pancreatic cancer cells aggressiveness via α4β1 integrin complexes and FAK signaling. *Int J Mol Sci*. **2022**;23(10):5459. doi: [10.3390/ijms23105459](https://doi.org/10.3390/ijms23105459)
114. Muniyan S, Haridas D, Chugh S, et al. MUC16 contributes to the metastasis of pancreatic ductal adenocarcinoma through focal adhesion mediated signaling mechanism. *Genes Cancer*. **2016**;7(3–4):110–124. doi: [10.18632/genesandcancer.104](https://doi.org/10.18632/genesandcancer.104)
115. Olson MT, Wojtynek NE, Talmon GA, et al. Development of a MUC16-targeted near-infrared fluorescent antibody conjugate for intraoperative imaging of pancreatic cancer. *Mol Cancer Ther*. **2020**;19(8):1670–1681. doi: [10.1158/1535-7163.MCT-20-0033](https://doi.org/10.1158/1535-7163.MCT-20-0033)
116. Nisenblat V, Prentice L, Bossuyt PM, et al. Combination of the non-invasive tests for the diagnosis of endometriosis. *Cochrane Database Syst Rev*. **2016**;7:p. CD012281.
117. Hirsch M, Duffy J, Davis CJ, et al. International collaboration to harmonise outcomes and measures for endometriosis. Diagnostic accuracy of cancer antigen 125 for endometriosis: a systematic review and meta-analysis. *BJOG: Int J Obstet Gy*. **2016**;123(11):1761–1768. doi: [10.1111/1471-0528.14055](https://doi.org/10.1111/1471-0528.14055)
118. Oliveira MAP, Raymundo TS, Soares LC, et al. How to use CA-125 more effectively in the diagnosis of deep endometriosis. *Biomed Res Int*. **2017**;2017:9857196. doi: [10.1155/2017/9857196](https://doi.org/10.1155/2017/9857196)
119. Chen FP, Soong YK, Lee N, et al. The use of serum CA-125 as a marker for endometriosis in patients with dysmenorrhea for monitoring therapy and for recurrence of endometriosis. *Acta Obstet Gynecol Scand*. **1998**;77:665–670. doi: [10.1034/j.1600-0412.1998.770615.x](https://doi.org/10.1034/j.1600-0412.1998.770615.x)
120. Won S, Cho YJ, Lee N, et al. Atypical endometriosis is related to a higher recurrence rate. *Eur J Obstet Gynecol Reprod Biol*. **2020**;254:44–51. doi: [10.1016/j.ejogrb.2020.08.054](https://doi.org/10.1016/j.ejogrb.2020.08.054)
121. Graziano A, Lo Monte G, Piva I, et al. Diagnostic findings in adenomyosis: a pictorial review on the major concerns. *Eur Rev Med Pharmacol Sci*. **2015**;19:1146–1154.
122. Kil K, Chung JE, Pak HJ, et al. Usefulness of CA125 in the differential diagnosis of uterine adenomyosis and myoma. *Eur J Obstet Gynecol Reprod Biol*. **2015**;185:131–135. doi: [10.1016/j.ejogrb.2014.12.008](https://doi.org/10.1016/j.ejogrb.2014.12.008)
123. Abdelazim IA, AbuFaza M, Hamed MES, et al. Severe adenomyosis with unexpectedly high CA-125: report of a rare case. *Prz Menopauzalny*. **2020**;19:144–146. doi: [10.5114/pm.2020.99610](https://doi.org/10.5114/pm.2020.99610)
124. Uchino K, Shimizu T, Mizukami H, et al. Nonbacterial thrombotic endocarditis complicated by cerebral infarction in a patient with adenomyosis with high serum CA125 level: a case report. *J Stroke Cerebrovasc Dis*. **2018**;27:e42–45. doi: [10.1016/j.jstrokecerebrovasdis.2017.09.064](https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.064)
125. Zheng R, Zeng D, Wan TT, et al. Predisposing factors for predicting the therapeutic response of adenomyosis after uterine artery embolization: serum CA125 levels and accompanying endometriosis. *Diagn Interv Radiol*. **2018**;24(6):364–371. doi: [10.5152/dir.2018.17479](https://doi.org/10.5152/dir.2018.17479)
126. Mu Y, Hu X, He J, et al. Serum levels of vascular endothelial growth factor and cancer antigen 125 are related to the prognosis of adenomyosis patients after interventional therapy. *Int J Clin Exp Med*. **2015**;8:9549–9554.
127. Zou K, Fu Y, Yang R, et al. CuO-ZnO heterojunction derived from Cu-doped ZIF-8: a new photoelectric material for ultrasensitive PEC immunoassay of CA125 with near-zero background noise. *Anal Chim Acta*. **2020**;1099:75–84. doi: [10.1016/j.aca.2019.11.054](https://doi.org/10.1016/j.aca.2019.11.054)
128. Xu X, Ji J, Chen P, et al. Salt-induced gold nanoparticles aggregation lights up fluorescence of DNA-silver nanoclusters to monitor dual cancer markers carcinoembryonic antigen and carbohydrate antigen 125. *Anal Chim Acta*. **2020**;1125:41–49. doi: [10.1016/j.aca.2020.05.027](https://doi.org/10.1016/j.aca.2020.05.027)
129. Rebelo TSCR, Costa R, Brandão ATSC, et al. Molecularly imprinted polymer SPE sensor for analysis of CA-125 on serum. *Anal Chim Acta*. **2019**;1082:126–135. doi: [10.1016/j.aca.2019.07.050](https://doi.org/10.1016/j.aca.2019.07.050)
130. Olson MT, Aguilar EN, Brooks CL, et al. Preclinical evaluation of a humanized, near-infrared fluorescent antibody for fluorescence-guided surgery of MUC16-expressing pancreatic

- cancer. *Mol Pharm.* 2022;19(10):3586–3599. doi: [10.1021/acs.molpharmaceut.2c00203](https://doi.org/10.1021/acs.molpharmaceut.2c00203)
131. Rao TD, Fernández-Tejada A, Axelrod A, et al. Antibodies against specific MUC16 glycosylation sites inhibit ovarian cancer growth. *ACS Chem Biol.* 2017;12(8):2085–2096. doi: [10.1021/acscchembio.7b00305](https://doi.org/10.1021/acscchembio.7b00305)
132. Yeku OO, Rao TD, Lester I, et al. Bispecific T-cell engaging antibodies against MUC16 demonstrate efficacy against ovarian cancer in monotherapy and in combination with PD-1 and VEGF inhibition. *Front Immunol.* 2021;12:663379. doi: [10.3389/fimmu.2021.663379](https://doi.org/10.3389/fimmu.2021.663379)
133. Crawford A, Haber L, Kelly MP, et al. A mucin 16 bispecific T cell-engaging antibody for the treatment of ovarian cancer. *Sci Transl Med.* 2019;11:eaau7534. doi: [10.1126/scitranslmed.aau7534](https://doi.org/10.1126/scitranslmed.aau7534)
134. Sharma SK, Mack KN, Piersigilli A, et al. ImmunoPET of ovarian and pancreatic cancer with AR9.6, a novel MUC16-targeted therapeutic antibody. *Clin Cancer Res.* 2022;28(5):948–959. doi: [10.1158/1078-0432.CCR-21-1798](https://doi.org/10.1158/1078-0432.CCR-21-1798)