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Review Article

Obstetrics and Gynaecology Section

Advances in Tumour Biomarkers for Screening, Diagnosis and Management of Ovarian Malignancies

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ABSTRACT

Ovarian cancer is one of most deadly malignancies in women, accounting for 1,52,000 deaths annually worldwide. Most ovarian malignancies are diagnosed at advanced stages when they have already metastasised to distant sites. Many researches are still under way to find means of detecting this malignancy at an early stage, so as to improve overall survival rates associated with it. One such way is use of serum biomarkers, which can help to some extent in detecting these cancers at an early stage as well as to follow-up patients during chemotherapy, after surgery and for detection of recurrent/persistent disease. Present review throws light on some of these novel biomarkers that help in detection and follow-up of women with ovarian cancers.

Keywords: Antibodies, Cancer, Chemotherapy

INTRODUCTION

Ovarian malignancy is seventh most commonly diagnosed and most lethal of all gynaecological cancers among women worldwide, accounting for an estimated 2,39,000 new cases and around 1,52,000 deaths annually [1-3]. The incidence of ovarian cancer varies according to geographic regions with maximum cases in developed countries, including North America and Central and Eastern Europe (>8 per 1,00,000 cases), intermediate in South America (5.8 per 1,00,000 cases) and lowest number in Asia and Africa (≤3 per 1,00,000 cases) [1,4-6].

In India, ovarian cancer is the third leading gynaecological cancer, after cervical and breast cancers [7]. The incidence rate in India, during 2001-2006, ranges between 0.9-8.4 per 1,00,000, cases. However, it has been observed that there is a steady increase in age standardised prevalence rate of ovarian cancer by around 3% per year in different state registries [8,9]. Also, it was observed that the incidence increasis sharply from 35 years of age and reaches a peak at around 55-64 years [8,10].

Most of the ovarian cancers usually present at an advanced stage when overall five year survival rate is only 29%. Very few cases (15%) are diagnosed at an early stage with localised tumour (stage 1), when five year survival rate can be as high as 92% [11]. Despite of various screening methods available till date, the overall five year relative survival rate ranges between 30-40% worldwide with only a very small increase of 2-4% in survival rates since 1995 [1]. Moreover, a woman's lifetime risk of having ovarian cancer is around 1 in 75, and her risk of dying due to disease is 1 in 100 indicating a large burden of disease and deaths due to it. One of the major issues why ovarian malignancies are diagnosed at a late stage is lack of specific symptoms and effective screening or diagnostic techniques [11-13]. Ovarian cancer usually remains asymptomatic in its early stages; patients present at an advanced stage with abdominal distension or mass, gastrointestinal symptoms like dyspepsia, bloating, loss of appetite and symptoms related to tumour metastasis [13]. Around 60-70% of women with ovarian cancer at the time of diagnosis are already in Stage III-IV or with abdominal metastasis, resulting in a poor five year survival rate and less than 25% are at Stage I, when the disease is localised to ovaries itself [13-15].

Furthermore, if ovarian cancer is diagnosed at an early stage (Stage I) the overall five year survival rate can be as high as >90% and most of these women can be cured by surgery alone [16]. Hence, early diagnosis of ovarian cancer is most important for improving the five year survival rate of women suffering from this dreadful condition [13]. This can be achieved to some extent by use of specific and sensitive ovarian tumour biomarkers. Studies are still underway for development of such biomarkers that can help in detection of ovarian cancers at an early stage. The present review discusses some of the serum biomarker which can help in early detection of ovarian cancer, either alone or in combination for better management and to decrease the overall morbidity and mortality associated with this disease. Recent literature related to ovarian malignancy and its detection using biomarkers was searched from several english journals, peer-reviewed articles on Pubmed, google scholar, MEDLINE and various governmental agencies till 2017.

Serum Tumour Markers

Cancer antigen (CA)-125: The CA-125 was the first circulating biomarker for ovarian cancer and its recognition in 1981, initiated the research for other biomarkers for ovarian carcinoma [17,18]. Till date, it is one of the most extensively studied biomarker for early detection of ovarian malignancy, and is valuable for both early detection and monitoring of disease after surgery or chemotherapy [18,19]. It is a membrane bound protein found on the surface of cells that go through metaplastic changes into a müllerian type epithelium, or is released in soluble form in body fluids [18,20].

The exact role of CA-125 in body remains poorly understood. The unusual features of oligosaccharides linked to CA-125 may play role in cell mediated immune response [18,21]. It was observed that CA-125 decreases the complement lysis of antibody sensitised cells [18,22]. Also, the bisecting type biantennary oligosaccharides attached to CA-125 can cause inhibition of cytotoxic responses of human Natural Killer (NK) cells and this inhibition is directly proportional to severe reduction in CD16 (FcγRIII) expression on cell surface of NK cells [18,23,24].

Furthermore, it was found by various studies that CA-125 also binds to mesothelin, which is a 40 kDa protein present over the surface of cancer cells of ovaries, lungs and pancreas and also on normal mesothelial cells [18,25,26]. This interaction promotes attachment of

tumour cells expressing CA-125 to the peritoneal lining expressing mesothelin, thereby explaining their role in peritoneal deposits seen in women with ovarian malignancy [18,27,28].

Despite of all this, CA-125 is still the only best proven biomarker to detect ovarian cancer at an early stage even before onset of clinical symptoms [13-15,29]. Its levels are detected using double determinant Enzyme Linked Immunosorbant Assay (ELISA) tests that detects two monoclonal antibodies (Anti-CA-125) directed against the epitope groups M11 and OC125 [18,30].

Haptoglobin: Haptoglobin is an acute phase tetrameric glycoprotein with two α and β dimers. The β-chains are identical in all haptoglobin molecules, while differences in α-chains result in polymorphisms of haptoglobin [31]. The main phenotypes are: haptoglobin 1-1, haptoglobin 2-2, and heterozygous haptoglobin 2-1 [32]. Haptoglobin is mainly associated with regulation of immune response and is one of the most abundant glycoproteins secreted by liver. Elevated levels are usually observed in infections, inflammation, and in various malignancies, like lung and bladder cancers, leukaemias, breast cancers, malignant lymphoma, urogenital tumours, and oesophageal Squamous Cell Carcinoma (SCC) [32-38].

Furthermore, the serum and ascitic fluid haptoglobin levels are significantly higher in patients with advanced epithelial ovarian cancer with overall poor survival [31,32,39]. Six different isoforms of haptoglobin-1 were observed in the serum of women with epithelial cell ovarian cancer, and these were found at very high concentrations in early stages, suggesting that haptoglobin-1 can be used as biomarker for early diagnosis of epithelial cell ovarian cancer [32]. Hence, the preoperative levels of haptoglobin can serve as an independent prognostic factor in women with epithelial cell ovarian cancers [31] and also helps in monitoring response to treatment, similar to CA-125 [32].

Osteopontin: Osteopontin (OPN) is an extracellular matrix glycoprotein that plays as important role in various cellular processes, like wound healing, inflammation, immune mechanism and tumourigenesis [40,41]. Its levels are usually overexpressed in women with ovarian cancer. In addition to this, it is also elevated in other human malignancies like malignant pleural mesothelioma, hepatocellular carcinoma and breast cancer [41-43]. Its use in diagnosis and assessing the prognosis of ovarian cancer has been studied most intensively by two recently published meta analysis, which revealed that serum OPN levels were significantly increased in women with ovarian cancers, indicating its potential role as biomarker for ovarian cancer [41,44].

Furthermore, it was observed that overall diagnostic sensitivity and specificity of OPN for ovarian cancer was 0.66 (95% CI, 0.51-0.78) and 0.88 (95% CI, 0.78-0.93), respectively [41]. Various studies have shown that the levels of OPN were significantly higher in women with advanced International Federation of Gynaecology and Obstetrics (FIGO) stages of ovarian cancer, indicating high diagnostic sensitivity of OPN for advanced ovarian cancers [45].

Hence, higher levels of OPN are usually associated with overall poor prognosis. Also, the disease free survival of patients is inversely related to OPN levels in various cancers [46,47]. There is a strong correlation between high OPN levels in tumour (82%) and plasma (100%) measurements and decreased mean survival time, indicating its role in patient stratification. Hence, in addition to a prognostic marker for survival, OPN is also a marker for grade, stage, and early progression of disease [46].

Human kallikreins: Kallikreins (hK) are group of 15 trypsin and chymotrypsin like secreted serine proteases, encoded by contiguous cluster of 15 structurally similar genes localised on chromosome 19q13.4 [48,49]. Several members of hK were found to be associated with ovarian cancers, of which hK6 and 10 are mainly elevated in cancer cells, serum and ascitic fluid of women with ovarian cancer and correlate best with disease prognosis. Other hK that may be related to ovarian cancer include hK4, 5, 7, 8, 9, 11, 13, 14 and 15 [50]. The most studied of all hK is hK3 also known as prostate specific antigen, and it is also the best known cancer biomarker for early diagnosis and management of several cancer types including prostate and ovarian carcinoma [49,51]. Various studies have shown that till now, 12hK genes were significantly up regulated in women with ovarian cancer, resulting in high hK protein levels in the tumour cells, ascitic fluid, and/or serum of these patients. Furthermore, it was found that this overexpression of hKs in ovarian cancer was also linked with patient prognosis [48,49]. According to a recent meta-analysis of 10 studies, hK acts as a mediator of tumourigenesis and it was found that positive hK expression was significantly associated with worse overall survival and progression free survival in women with ovarian malignancy [52]. The hK7 has recently been included as a part of ovarian cancer prognostic profile signature [53]. Also, the raised serum levels of hK5, hK6, hK8, hK10, hK11, and hK14 may help in the early diagnosis and management of women with ovarian malignancy [54-59].

Studies have shown that levels of human hK13 were raised in 50% of women with ovarian malignancy as compared to low levels in women with normal or benign ovarian tissue. Also, it was observed that levels of hK13 was associated with early stage disease, no residual tumour, and optimal debulking. Hence, hKs can act as an independent predictor for favourable outcome in women with ovarian cancers [60].

Bikunins: Bikunin is a heavily glycosylated, Kunitz type protease inhibitor, mainly found in human amniotic fluid. It is synthesised by liver cells and excreted in urine [61]. The exact function of bikunin is not clear, but is known to mediate suppression of tumour cell invasion and metastasis. This was evidenced by administration of bikunin in cancers, where it blocked tumour cell invasion by directly inhibiting tumour cell associated plasmin activity as well as by inhibiting urokinase type Plasminogen Activator (uPA) expression at gene and protein levels [62]. Furthermore, it was observed that there is a direct correlation between raised bikunin levels and decreased metastatic potential of primary tumour biopsies. Hence, low bikunin mRNA expression was associated with poor overall prognosis in women with ovarian cancer and this is independent of age at surgery, stage, size, histology, degree of differentiation of tumour and plasma CA-125 levels [63,64].

Therefore, preoperative plasma bikunin concentration may be used as a strong and independent favourable prognostic marker for screening of patients with ovarian cancers [63].

Human epididymis protein 4: Human epididymis protein 4 (HE4), was first discovered by Kirchhoff C et al., [65]. It belongs to "whey-acidic four disulfide core" family of proteins, which functions as proteinase inhibitors that decreasis the activity of serine proteases PRSS35 and PRSS23, responsible for degrading type I collagen that accumulates in kidney fibrosis [66,67]. The gene for HE4 known as WFDC2 is located on chromosome 20q12-13.1 [67,68].

Normally, HE4 is expressed over glandular epithelium of breast, female genital tract, epididymis, vas deferens, distal renal tubules, respiratory epithelium, colonic mucosa, and salivary glands, whereas, among different tumour sites, the maximum levels were observed in ovarian cancers followed by lung adenocarcinoma and lowest in breast, gastric, transitional cell, and pancreatic carcinomas [66,69,70]. Recent studies have shown that the highest levels of HE4 were found in ovarian cancer in women and in lung cancer in men [66,71]. Furthermore, it was found that HE4 plays an important role in migration and adhesion of ovarian tumour cells. Various in vitro studies have shown that knockdown of HE4 results in inhibition of tumour growth [66,72]. It was in 2003, when HE4 for the first time was identified as a potential secreted tumour marker due to its overexpression in ovarian cancer tissue as compared to normal ovarian tissue and other carcinomas [66,73,74]. Raised

levels of HE4 correlates with the aggressiveness of ovarian cancer, overall poor prognosis and survival [66,75]. Also, the higher levels were found to be associated with increase in FIGO stage, grade of tumour, preoperative CA-125 levels, and residual tumour as well as platinum resistance [66,75,76].

A recently FDA approved algorithm known as Risk Of Malignancy Algorithm (ROMA) combines CA-125-HE4 marker panel in menopausal women for differentiating malignant from benign ovarian masses [66,77]. It was found that ROMA has a better diagnostic ability than CA-125 alone, with a sensitivity and specificity of 78.9% and 85.9% respectively. Also, it was observed that HE4 is better than CA-125 in detecting borderline tumours, early stage ovarian and tubal cancers, and in predicting recurrent epithelial ovarian cancers even when it is used alone [66,78,79]. Hence, HE4 may prove to have better sensitivity and specificity in detection of ovarian cancers as compared with CA-125 [73,80,81].

Vascular endothelial growth factor: Vascular Endothelial Growth Factor (VEGF) is a 45 kDa heparin binding homodimeric glycoprotein that plays an important role in physiological and pathological angiogenesis [82,83]. It is a family of cytokines that includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, Placenta Growth Factor (PlGF), VEGF-E, and VEGF-F (snake venom VEGFs) [84]. It plays an important role in angiogenesis, haematopoiesis, haemodynamics, and vascular homeostasis. It acts as an endothelial cell mitogen, thereby promoting vascular endothelial cells regrowth during physiological and tumour angiogenesis [85]. VEGF is important for normal functioning of ovaries, as ovary is different from other endocrine organs of body in that it undergoes repetitive cycles of angiogenesis within its various glandular compartments [82,86]. High intrafollicular levels of VEGF were observed during the initial part of ovulatory cycle, with peak concentrations occurring before onset of luteal phase [82,87]. Furthermore, ovarian malignancies are highly vascularised tumours and this vascularisation is dependent on VEGF mediated angiogenesis [88]. Also, VEGF is implicated in various other ovarian pathologies [82,89].

Since, VEGF mediates a crucial, early event of tumour angiogenesis, its overexpression is associated with greater tumour growth, aggression, as well as poor overall survival [90,91]. Moreover, it was observed that overexpression of VEGF can result in transformation of normal, functional ovarian tissue into ascites producing, malignant tissue through an autocrine loop [82,88,92,93]. Hence, overexpression of intratumoural VEGF in women with ovarian cancer correlates with poor prognosis, enhanced disease progression, poor overall survival and as a biomarker of response to platinum based chemotherapy [82,92,94-97].

The VEGF can therefore act as a serological biomarker for diagnosis and prediction of prognosis in women with ovarian cancer [82,98]. Recent studies have shown that women with ovarian tumours positive for VEGF and Cyclooxygenase 2 (COX 2) staining have decreased overall survival and may get benefit from antiangiogenesis targeted therapy [99].

Mesothelin: Mesothelin is a 40 kDa glycosylphosphatidylinositol linked protein expressed over the surface of normal peritoneal, pleural, and pericardial mesothelial cells, but is also highly expressed in mesothelioma and other human malignancies like ovarian, pancreatic and some SCCs [100,101]. It is encoded by mesothelin gene as a 69 kDa precursor protein with hydrophobic sequence at the carboxyl end that is replaced by phosphatidylinositol. This glycosylphosphatidylinositol linkage helps in anchoring mesothelin to cell membrane [102,103]. Mesothelin is produced in three isoforms that enter the circulation, either through shedding of membrane bound portion (variants 1 and 2) or by a frameshift mutation (variant 3). Of all these variants, variant 1 is principally expressed and released from membrane [100,103]. The exact function of mesothelin is not clear, but it has been observed that it binds to CA-125, thereby facilitating cellular adhesion and signaling [104]. In this manner, it may play an important role in tumour adhesion and metastasis [101,105].

It is overexpressed in ovarian cancer tissues and a soluble form can be easily detected in blood of women suffering from ovarian malignancy. Elevated levels are found in 40-67% of such women with ovarian cancer [101,106]. Also, the overexpression is associated with a poor overall outcome [102]. Hence, it can act as an important biomarker for diagnosis and assessing the prognosis of women with ovarian cancer.

B7-H4: B7-H4 or B7x or B7S1, belongs to B7 family which is normally expressed over surface of activated antigen presenting cells [107]. It was first recognised in 2003, and its action is mediated through an unidentified CD28 family receptor present over activated T cells and activation of this B7-H4 pathway is responsible for inhibition of T cell mediated immune response [108,109]. It was also observed that B7-H4 plays an important role in regulation of T cell mediated immune response by inhibiting T cell proliferation, cytokine secretion, and development of cytotoxicity [108].

Of B7 family, B7-H1 {also known as Programmed Death-1-Ligand 1 (PD-L1)} and B7-H4, are most important costimulatory molecules responsible for T cell activation [110]. Moreover, various recent studies have observed that they may also act as negative regulatory factors in antitumour immune response of the body [110-112]. It was found that B7-H4 is highly expressed in various human tumours, including breast, ovarian, lung, pancreatic, gastric and urothelial cell carcinoma [108,113-118]. Also, high levels of B7 especially B7-H1 and B7-H4 in tumour cells of these malignancies are closely associated with disease progression and prognosis [108,110,119].

Furthermore, the levels of B7-H4 were very low in normal ovaries and in benign tumours whereas 50% of early stage and 66% of late stage cancers have overexpression of B7-H4 [120]. Also, it was found that women with high coinciding levels of B7-H1 and B7-H4 had poor survival, and increased risk of relapse. Hence, over expression of B7-H1 and B7-H4 in tumour tissues can be used as a tumour marker with negative prognostic effect for epithelial cell ovarian cancer and can prove as a potential immunotherapeutic target for these patients [110].

Lysophosphatidic acid: Lysophosphatidic Acid (LPA) is a small bioactive phospholipid detected in ascitic fluid and blood of women with ovarian cancer [121]. The LPA causes stimulation of G protein coupled receptors of endothelial differentiation gene family resulting in cell proliferation, cell migration, cell survival, platelet aggregation, smooth muscle cell contraction, wound healing and alteration in morphology and differentiation of cells [121,122]. This LPA mediated pathway is significantly linked with tumour growth and metastasis in various human cancers. LPA is generated from lysophospholipids present in serum and plasma, and from phosphatidic acid in platelets and cancer cells [123]. Also, the ovarian tumour cells are a major source of LPA and Autotaxin (ATX) [124]. Hence, the plasma levels of LPA are robustly associated with presence of ovarian tumours and the levels are significantly higher in women with ovarian cancers as compared to those with benign ovarian lesions [121,125].

Furthermore, various studies have found that the increased LPA levels are also associated with increased expression of other important metastasis promoters necessary for ovarian cancer progression [121,126]. Also, higher the plasma LPA levels; more is the FIGO staging of ovarian cancer. This is not affected by histological subtype and grade of ovarian cancer. Hence, the plasma LPA levels can prove as a useful marker for detection of ovarian cancer, especially in its early stages [125].

Human serine protease prostasin (PRSS8): Human prostasin also known as channel activating protease 1, a 40 KDa trypsin like proteinase, is a glycosyl phosphatidyl inositol anchored extracellular serine protease encoded by PRSS8 gene, located on

chromosome 16p11.2. It is normally expressed over epithelial cells and ducts of prostate glands and was first isolated from seminal fluid [127]. Being a channel activating protease, it is present in all those tissues that absorb sodium and acts as a proteolytic activator of epithelial sodium channel and helps in regulating sodium balance, thus playing an important role in regulating blood pressure [127-130].

Many human cancers show unusual expression of prostasin like urinary bladder, uterine, prostate, gastric and ovarian cancers [131]. Furthermore, it was observed that prostasin initiates cleavage of extracellular domain of epidermal growth factor on epithelial cells, resulting in continuous phosphorylation of receptor, thereby triggering metastasis of tumour. Hence, the levels of prostasin were found to be significantly higher in patients with advanced stage ovarian cancer. The levels were 120-410 times higher in advanced stage ovarian cancer patients as compared to normal ones [127,132]. Though, the prostasin is overexpressed in all stages of ovarian cancer, but levels change considerably from early to late stages. Peak levels were usually found at stage II and III and then decreasis sharply at stage IV (level being still slightly higher than in normal tissue) [130,133]. Moreover, prostatin is usually not present in normal ovarian tissues, but is upregulated from the very beginning of the disease. As there is overexpression of prostatin in the ovarian tissues from early stages and low grades, it can thus be used as a complementary biomarker to CA-125 for early detection of ovarian cancer [127,130,132].

Macrophage colony stimulating factor: Macrophage-Colony Stimulating Factor (M-CSF) also known as a Colony Stimulating Factor 1 (CSF-1) is a cytokine that regulates growth, stimulates proliferation and differentiation of phagocytic cells including neutrophils or macrophages [134]. Furthermore, it is also known to play a major role in pathogenesis of various human cancers, including breast, lung, pancreatic, cervical, and ovarian cancers [135-140]. Moreover, it was found that M-CSF and its receptor gene, c-fms, were overexpressed in various gynaecological malignancies, and this coexpression might be involved in progression of disease to metastatic state, and is usually associated with overall poor prognosis [140-142]. Furthermore, M-CSF is a potent chemoattractant for monocytes, which produces factors like Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumour Necrosis Factor (TNF) that causes increased proliferation of ovarian tumour cells. The clinical specimens from parient with metastatic ovarian cancer reveal strong immunostaining for both M-CSF and its receptor as compared to those with noninvasive borderline tumours or benign ovarian tissue [135,141,142]. Hence, M-CSF can be used to assess progress of disease and overall prognosis of patients with ovarian cancers.

OVA1: OVA 1 is a five protein biomarker panel approved by FDA in 2009 [143,144]. It utilises a combination of five biomarkers; CA-125-II, apolipoprotein A1, transthyretin, beta-2 microglobulin, and transferrin identified through serum proteomics [144,145]. Two of these biomarkers (CA-125 II, β-microglobulin) are upregulated and three are downregulated (apolipoprotein A1, prealbumin, transferring) in women with ovarian cancers. Serum levels of these biomarkers are compiled using a computer program giving a final score of 0 to10. The values ≥5.0 in premenopausal and ≥4.4 in postmenopausal women are considered high risk groups [146]. Recent multicenter study has shown high sensitivity and specificity of OVA1 test in diagnosis of ovarian cancer of 96% (91% in FIGO I/II) and 51% respectively.

Recently, in 2016, the FDA cleared another new generation OVA1 test known as Overa® that essentially combines two multivariate index assay tests and has a high diagnostic sensitivity with improved specificity [147]. The biomarkers included in this test are CA-125-II, HE4, apolipoprotein A-1, follicle stimulating hormone, and transferring [144].

CONCLUSION

The main aim of using tumour biomarkers is to diagnose ovarian cancers at an early stage, so as to reduce the overall burden of morbidity and mortality associated with this disease. Although, none of the biomarkers are perfect in diagnosing ovarian cancer at an early stage. With the search of newer biomarkers, we can expect in future that ovarian malignancies can be diagnosed at as earlier stage.

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REFERENCES

[1] Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017;14(1):9-32.
[2] Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, et al. SEER Cancer statistics review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
[3] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 (Internet). Lyon, France: International Agency for Research on Cancer. 2014.
[4] Ferlay JSH, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v 1.2: Cancer Incidence, Mortality, and Prevalence Worldwide: IARC Cancer Base No. 10. Lyon, France: International Agency for Research on Cancer. 2008 (2011-12-18).
[5] Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin. 2000;50(1):7-33.
[6] Shanmughapriya S, Nachiappan V, Natarajaseenivasan K. BRCA1 and BRCA2 mutations in the ovarian cancer population across race and ethnicity: special reference to Asia. Oncology. 2013;84(4):226-32.
[7] Basu P, De P, Mandal S, Ray K, Biswas J. Study of 'patterns of care' of ovarian cancer patients in a specialized cancer institute in Kolkata, eastern India. Indian J Cancer. 2009;46(1):28-33.
[8] Murthy NS, Shalini S, Suman G, Pruthvish S, Mathew A. Changing trends in incidence of ovarian cancer-the Indian scenario. Asian Pac J Cancer Prev. 2009;10(6):1025-30.
[9] Shanmughapriya SG, Senthilkumar G, Arun S, Das BC, Natarajaseenivasan K. Risk factors for epithelial ovarian carcinoma in india: a case control study in low-incidence population. Int J Cancer Res. 2016;12:61-68.
[10] Saini SK, Srivastava S, Singh Y, Dixit AK, Prasad SN. Epidemiology of epithelial ovarian cancer, a single institution-based study in India. Clin Cancer Investig J. 2016;5(1):20-24.
[11] Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER Cancer statistics review, 1975_2008, National Cancer Institute. Bethesa, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
[12] Chornokur G, Amankwah EK, Schildkraut JM, Phelan CM. Global ovarian cancer health disparities. Gynaecol Oncol. 2013;129(1):258-64.
[13] Dong X, Men X, Zhang W, Lei P. Advances in tumour markers of ovarian cancer for early diagnosis. Indian J Cancer. 2014;51(Suppl S3):72-76.
[14] Colombo N, Peiretti M, Garbi A, Carinelli S, Marini C, Sessa C. Non-epithelial ovarian cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(7):vii20-26.
[15] Rein BJ, Gupta S, Dada R, Safi J, Michener C, Agarwal A. Potential markers for detection and monitoring of ovarian cancer. J Oncol. 2011;2011:475983.
[16] Colombo N, Van Gorp T, Parma G, Amant F, Gatta G, Sessa C, et al. Ovarian cancer. Crit Rev Oncol Hematol. 2006;60(2):159-79.
[17] Bast RC, Feeney M, Lazarus H, Nadler LM, Colvin RB, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Invest. 1981;68(5):1331-37.
[18] Scholler N, Urban N. CA125 in ovarian cancer. Biomark Med. 2007;1(4):513-23.
[19] Jacobs IJ, Menon U. Progress and challenges in screening for early detection of ovarian cancer. Mol Cell Proteomics. 2004;3(4):355-66.
[20] Feeley KM, Wells M. Precursor lesions of ovarian epithelial malignancy. Histopathology. 2001;38(2):87-95.
[21] Kui Wong N, Easton RL, Panico M, Sutton-Smith M, Morrison JC, Lattanzio FA, et al. Characterization of the oligosaccharides associated with the human ovarian tumour marker CA125. J Biol Chem. 2003;278(31):28619-34.
[22] Murdoch WJ, Van Kirk EA, Smedts AM. Complement-inhibiting effect of ovarian cancer antigen CA-125. Cancer Lett. 2006;236(1):54-57.
[23] Yoshimura M, Ihara Y, Ohnishi A, Ijuhin N, Nishiura T, Kanakura Y, et al. Bisecting N-acetylglucosamine on K562 cells suppresses natural killer cytotoxicity and promotes spleen colonization. Cancer Res. 1996;56(2):412-18.
[24] Belisle JA, Gubbels JA, Raphael CA, Migneault M, Rancourt C, Connor JP, et al. Peritoneal natural killer cells from epithelial ovarian cancer patients show an altered phenotype and bind to the tumour marker MUC16 (CA125). Immunology. 2007;122(3):418-29.
[25] Hassan R, Laszik ZG, Lerner M, Raffeld M, Postier R, Brackett D. Mesothelin is overexpressed in pancreaticobiliary adenocarcinomas but not in normal pancreas and chronic pancreatitis. Am J Clin Pathol. 2005;124(6):838-45.

[26] Galloway ML, Murray D, Moffat DF. The use of the monoclonal antibody mesothelin in the diagnosis of malignant mesothelioma in pleural biopsies. Histopathology. 2006;48(6):767-69.
[27] Gubbels JA, Belisle J, Onda M, Rancourt C, Migneault M, Ho M, et al. Mesothelin-MUC16 binding is a high affinity, N-glycan dependent interaction that facilitates peritoneal metastasis of ovarian tumours. Mol Cancer. 2006;5(1):50.
[28] Scholler N, Garvik B, Hayden-Ledbetter M, Kline T, Urban N. Development of a CA125-mesothelin cell adhesion assay as a screening tool for biologics discovery. Cancer Lett. 2007;247(1):130-36.
[29] Díaz-Padilla I, Razak AR, Minig L, Bernardini MQ, María Del Campo J. Prognostic and predictive value of CA-125 in the primary treatment of epithelial ovarian cancer: potentials and pitfalls. Clin Transl Oncol. 2012;14(1):15-20.
[30] Scholler N, Crawford M, Sato A, Drescher CW, O'Briant KC, Kiviat N, et al. Bead-based ELISA for validation of ovarian cancer early detection markers. Clin Cancer Res. 2006;12(7 Pt 1):2117-24.
[31] Zhao C, Annamalai L, Guo C, Kothandaraman N, Koh SC, Zhang H, et al. Circulating haptoglobin is an independent prognostic factor in the sera of patients with epithelial ovarian cancer. Neoplasia. 2007;9(1):01-07.
[32] Mandato VD, Magnani E, Abrate M, Casali B, Nicoli D, Farnetti E, et al. Haptoglobin phenotype and epithelial ovarian cancer. Anticancer Res. 2012;32(10):4353-58.
[33] Benkmann HG, Hanssen HP, Ovenbeck R, Goedde HW. Distribution of alpha-1-antitrypsin and haptoglobin phenotypes in bladder cancer patients. Hum Hered. 1987;37(5):290-93.
[34] Mitchell RJ, Carzino R, Janardhana V. Associations between the two serum proteins haptoglobin and transferrin and leukaemia. Hum Hered. 1988;38(3):144-50.
[35] Awadallah S, Atoum M. Haptoglobin polymorphisms in breast cancer patients form Jordan. Clin Chim Acta. 2004;341(1-2):17-21.
[36] Epelbaum R, Shalitin C, Segal R, Valansi C, Arselan I, Faraggi D, et al. Haptoglobin-related protein as a serum marker in malignant lymphoma. Pathol Oncol Res. 1998;4(4):271-76.
[37] Dunzendorfer U, Jung K, Ohlenschläger G. Transferrin, C3 complement, haptoglobin, plasminogen and alpha 2-microglobulin in patients with urogenital tumours. Eur Urol. 1980;6(4):232-36.
[38] An JY, Fan ZM, Zhuang ZH, Qin YR, Gao SS, Li JL, et al. Proteomic analysis of blood level of proteins before and after operation in patients with oesophageal squamous cell carcinoma at high-incidence area in Henan province. World J Gastroenterol. 2004;10(22):3365-68.
[39] Ahmed N, Barker G, Oliva KT, Hoffmann P, Riley C, Reeve S, et al. Proteomic-based identification of haptoglobin-1 precursor as a novel circulating biomarker of ovarian cancer. Br J Cancer. 2004;91(1):129-40.
[40] Ahmed M, Behera R, Chakraborty G, Jain S, Kumar V, Sharma P, et al. Osteopontin: a potentially important therapeutic target in cancer. Expert Opin Ther Targets. 2011;15(9):1113-26.
[41] Hu ZD, Wei TT, Yang M, Ma N, Tang QQ, Qin BD, et al. Diagnostic value of osteopontin in ovarian cancer: a meta-analysis and systematic review. PLoS ONE. 2015;10(5): e0126444.
[42] Hu ZD, Liu XF, Liu XC, Ding CM, Hu CJ. Diagnostic accuracy of osteopontin for malignant pleural mesothelioma: a systematic review and meta-analysis. Clin Chim Acta. 2014;433:44-48.
[43] Cheng J, Wang W, Sun C, Li M, Wang B, Lv Y. Meta-analysis of the prognostic and diagnostic significance of serum/plasma osteopontin in hepatocellular carcinoma. J Clin Gastroenterol. 2014;48(9):806-14.
[44] Wang YD, Chen H, Liu HQ, Hao M. Correlation between ovarian neoplasm and serum levels of osteopontin: a meta-analysis. Tumour Biol. 2014;35(12):11799-808.
[45] Moszynski R, Szubert S, Szpurek D, Michalak S, Sajdak S. Role of osteopontin in differential diagnosis of ovarian tumours. J Obstet Gynaecol Res. 2013;39(11):1518-25.
[46] Weber GF, Lett GS, Haubein NC. Osteopontin is a marker for cancer aggressiveness and patient survival. Br J Cancer. 2010;103(6):861-69.
[47] Weber GF. The cancer biomarker osteopontin: combination with other markers. Cancer Genomics Proteomics. 2011;8(6):263-88.
[48] Borgoño CA, Michael IP, Diamandis EP. Human tissue kallikreins: physiologic roles and applications in cancer. Mol Cancer Res. 2004;2(5):257-80.
[49] Borgoño CA, Kishi T, Scorilas A, Harbeck N, Dorn J, Schmalfeldt B, et al. Human kallikrein 8 protein is a favourable prognostic marker in ovarian cancer. Clin Cancer Res. 2006;12(5):1487-93.
[50] Oikonomopoulou K, Scorilas A, Michael IP, Grass L, Soosaipillai A, Rosen B, et al. Kallikreins as markers of disseminated tumour cells in ovarian cancer-a pilot study. Tumour Biol. 2006;27(2):104-14.
[51] Diamandis EP, Yousef GM. Human tissue kallikreins: a family of new cancer biomarkers. Clin Chem. 2002;48(8):1198-205.
[52] Wu Y, Lu M, Zhou Q. Kallikrein expression as a prognostic factor in ovarian cancer: a systematic review and meta-analysis. J BUON. 2015;20(3):855-61.
[53] Spentzos D, Levine DA, Ramoni MF, Joseph M, Gu X, Boyd J, et al. Gene expression signature with independent prognostic significance in epithelial ovarian cancer. J Clin Oncol 2004;22(23):4700-10.
[54] Yousef GM, Polymeris ME, Grass L, Soosaipillai A, Chan PC, Scorilas A, et al. Human kallikrein 5: a potential novel serum biomarker for breast and ovarian cancer. Cancer Res. 2003;63(14):3958-65.
[55] Diamandis EP, Scorilas A, Fracchioli S, Van Gramberen M, De Bruijn H, Henrik A, et al. Human kallikrein 6 (hK6): a new potential serum biomarker for diagnosis and prognosis of ovarian carcinoma. J Clin Oncol. 2003;21(6):1035-43.
[56] Kishi T, Grass L, Soosaipillai A, Scorilas A, Harbeck N, Schmalfeldt B, et al. Human kallikrein 8, a novel biomarker for ovarian carcinoma. Cancer Res. 2003;63(11):2771-74.
[57] Luo LY, Katsaros D, Scorilas A, Fracchioli S, Bellino R, van Gramberen M, et al. The serum concentration of human kallikrein 10 represents a novel biomarker for ovarian cancer diagnosis and prognosis. Cancer Res. 2003;63(4):807-11.
[58] Diamandis EP, Okui A, Mitsui S, Luo LY, Soosaipillai A, Grass L, et al. Human kallikrein 11: a new biomarker of prostate and ovarian carcinoma. Cancer Res. 2002;62(1):295-300.
[59] Borgoño CA, Grass L, Soosaipillai A, Yousef GM, Petraki CD, Howarth DH, et al. Human kallikrein 14: a new potential biomarker for ovarian and breast cancer. Cancer Res. 2003;63(24):9032-41.
[60] Scorilas A, Borgoño CA, Harbeck N, Dorn J, Schmalfeldt B, Schmitt M, et al. Human kallikrein 13 protein in ovarian cancer cytosols: a new favourable prognostic marker. J Clin Oncol. 2004;22(4):678-85.
[61] Thogersen IB, Enghild JJ. Biosynthesis of bikunin proteins in the human carcinoma cell line HepG2 and in primary human hepatocytes: Polypeptide assembly by glycosaminoglycan. J Biol Chem. 1995;270(31):18700-09.
[62] Kobayashi H, Suzuki M, Hirashima Y, Terao T. The protease inhibitor bikunin, a novel anti-metastatic agent. Biol Chem. 2003;384(5):749-54.
[63] Matsuzaki H, Kobayashi H, Yagyu T, Wakahara K, Kondo T, Kurita N, et al. Plasma bikunin as a favourable prognostic factor in ovarian cancer. J Clin Oncol. 2005;23(7):1463-72.
[64] Tanaka Y, Kobayashi H, Suzuki M, Kanayama N, Suzuki M, Yamakawa T, et al. Reduced bikunin gene expression as a factor of poor prognosis in ovarian carcinoma. Cancer. 2003;98(2):424-30.
[65] Kirchhoff C, Habben I, Ivell R, Krull N. A major human epididymis-specific cDNA encodes a protein with sequence homology to extracellular proteinase inhibitors. Biol Reprod. 1991;45(2):350-57.
[66] Simmons AR, Baggerly K, Bast RC Jr. The emerging role of HE4 in the evaluation of epithelial ovarian and endometrial carcinomas. Oncology (Williston Park). 2013;27(6):548-56.
[67] Steffensen KD, Waldstrøm M, Brandslund I, Lund B, Sørensen SM, Petzold M, et al. Identification of high-risk patients by human epididymis protein 4 levels during follow-up of ovarian cancer. Oncol Lett. 2016;11(6):3967-74.
[68] Clauss A, Lilja H, Lundwall A. A locus on human chromosome 20 contains several genes expressing protease inhibitor domains with homology to whey acidic protein. Biochem J. 2002;368(Pt 1):233-42.
[69] Galgano MT, Hampton GM, Frierson HF. Comprehensive analysis of HE4 expression in normal and malignant human tissues. Mod Pathol. 2006;19(6):847-53.
[70] O'Neal RL, Nam KT, LaFleur BJ, Barlow B, Nozaki K, Lee HJ, et al. Human epididymis protein 4 is up-regulated in gastric and pancreatic adenocarcinomas. Hum Pathol. 2013;44(5):734-42.
[71] Hertlein L, Stieber P, Kirschenhofer A, Krocker K, Nagel D, Lenhard M, et al. Human epididymis protein 4 (HE4) in benign and malignant diseases. Clin Chem Lab Med. 2012;50(12):2181-88.
[72] Lu R, Sun X, Xiao R, Zhou L, Gao X, Guo L. Human epididymis protein 4 (HE4) plays a key role in ovarian cancer cell adhesion and motility. Biochem Biophys Res Commun. 2012;419(2):274-80.
[73] Hellström I, Raycraft J, Hayden-Ledbetter M, Ledbetter JA, Schummer M, McIntosh M, et al. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. Cancer Res. 2003;63(13):3695-700.
[74] Drapkin R, von Horsten HH, Lin Y, Mok SC, Crum CP, Welch WR, 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):2162-69.
[75] Trudel D, Têtu B, Grégoire J, Plante M, Renaud MC, Bachvarov D, et al. Human epididymis protein 4 (HE4) and ovarian cancer prognosis. Gynaecol Oncol. 2012;127(3):511-15.
[76] Braicu EI, Fotopoulou C, Van Gorp T, Richter R, Chekerov R, Hall C, et al. Preoperative HE4 expression in plasma predicts surgical outcome in primary ovarian cancer patients: results from the OVCAD study. Gynaecol Oncol. 2013;128(2):245-51.
[77] Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynaecol Oncol. 2009;112(1):40-46.
[78] Jacob F, Meier M, Caduff R, Goldstein D, Pochechueva T, Hacker N, et al. No benefit from combining HE4 and CA125 as ovarian tumour markers in a clinical setting. Gynaecol Oncol. 2011;121(3):487-91.
[79] Innao P, Pothisuwan M, Pengsa P. Does human epididymis protein 4 (HE4) have a role in prediction of recurrent epithelial ovarian cancer. Asian Pac J Cancer Prev. 2016;17(9):4483-86.
[80] Zhen S, Bian LH, Chang LL, Gao X. Comparison of serum human epididymis protein 4 and carbohydrate antigen 125 as markers in ovarian cancer: a meta-analysis. Mol Clin Oncol. 2014;2(4):559-66.
[81] Gündüz UR, Gunaldi M, Isiksacan N, Gündüz S, Okuturlar Y, Kocoglu H. A new marker for breast cancer diagnosis, human epididymis protein 4: a preliminary study. Mol Clin Oncol. 2016;5(2):355-60.
[82] Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer Metastasis Rev. 2012;31(1-2):143-62.
[83] Chung AS, Ferrara N. Developmental and pathological angiogenesis. Annu Rev Cell Dev Biol. 2011;27:563-84.
[84] Yamazaki Y, Morita T. Molecular and functional diversity of vascular endothelial growth factors. Mol Divers. 2006;10(4):515-27.
[85] Chung AS, Lee J, Ferrara N. Targeting the tumour vasculature: insights from physiological angiogenesis. Nat Rev Cancer. 2010;10(7):505-14.

[86] Taylor PD, Wilson H, Hillier SG, Wiegand SJ, Fraser HM. Effects of inhibition of vascular endothelial growth factor at time of selection on follicular angiogenesis, expansion, development and atresia in the marmoset. Mol Hum Reprod. 2007;13(10):729-36.
[87] Kumaran GC, Jayson GC, Clamp AR. Antiangiogenic drugs in ovarian cancer. Br J Cancer. 2009;100(1):01-07.
[88] Ramakrishnan S, Subramanian IV, Yokoyama Y, Geller M. Angiogenesis in normal and neoplastic ovaries. Angiogenesis. 2005;8(2):169-82.
[89] Geva E, Jaffe RB. Role of vascular endothelial growth factor in ovarian physiology and pathology. Fertil Steril. 2000;74(3):429-38.
[90] Nakanishi Y, Kodama J, Yoshinouchi M, Tokumo K, Kamimura S, Okuda H, et al. The expression of vascular endothelial growth factor and transforming growth factor-beta associates with angiogenesis in epithelial ovarian cancer. Int J Gynaecol Pathol. 1997;16(3):256-62.
[91] Yamamoto S, Konishi I, Mandai M, Kuroda H, Komatsu T, Nanbu K, et al. Expression of vascular endothelial growth factor (VEGF) in epithelial ovarian neoplasms: correlation with clinicopathology and patient survival, and analysis of serum VEGF levels. Br J Cancer. 1997;76(9):1221-27.
[92] Masoumi-Moghaddam S, Amini A, Wei AQ, Robertson G, Morris DL. Vascular endothelial growth factor expression correlates with serum CA125 and represents a useful tool in prediction of refractoriness to platinum-based chemotherapy and ascites formation in epithelial ovarian cancer. Oncotarget. 2015;6(29):28491-501.
[93] Chen H, Ye D, Xie X, Chen B, Lu W. VEGF, VEGFRs expressions and activated STATs in ovarian epithelial carcinoma. Gynaecol Oncol. 2004;94(3):630-35.
[94] Kassim SK, El-Salahy EM, Fayed ST, Helal SA, Helal T, Azzam Eel-D, et al. Vascular endothelial growth factor and interleukin-8 are associated with poor prognosis in epithelial ovarian cancer patients. Clin Biochem. 2004;37(5):363-69.
[95] Chambers SK, Clouser MC, Baker AF, Roe DJ, Cui H, Brewer MA, et al. Overexpression of tumour vascular endothelial growth factor a may portend an increased likelihood of progression in a phase II trial of bevacizumab anderlotinib in resistant ovarian cancer. Clin Cancer Res. 2010;16(21):5320-28.
[96] Siddiqui GK, Elmasry K, Wong Te Fong AC, Perrett C, Morris R, Crow JC, et al. Prognostic significance of intratumoural vascular endothelial growth factor as a marker of tumour angiogenesis in epithelial ovarian cancer. Eur J Gynaecol Oncol. 2010;31(2):156-59.
[97] Siddiqui GK, Maclean AB, Elmasry K, Wong te Fong A, Morris RW, Rashid M, et al. Immunohistochemical expression of VEGF predicts response to platinum based chemotherapy in patients with epithelial ovarian cancer. Angiogenesis. 2011;14(2):155-61.
[98] Hefler LA, Zeillinger R, Grimm C, Sood AK, Cheng WF, Gadducci A, et al. Preoperative serum vascular endothelial growth factor as a prognostic parameter in ovarian cancer. Gynaecol Oncol. 2006;103(2):512-17.
[99] Whynott RM, Manahan P, Geisler JP. Vascular endothelial growth factor (VEGF) and cyclooxygenase 2 (COX 2) immunostaining in ovarian cancer. Eur J Gynaecol Oncol. 2016;37(2):164-66.
[100] Hollevoet K, Reitsma JB, Creaney J, Grigoriu BD, Robinson BW, Scherpereel A, et al. Serum mesothelin for diagnosing malignant pleural mesothelioma: an individual patient data meta-analysis. J Clin Oncol. 2012;30(13):1541-49.
[101] Madeira K, Dondossola ER, Farias BF, Simon CS, Alexandre MC, Silva BR, et al. Mesothelin as a biomarker for ovarian carcinoma: a meta-analysis. An Acad Bras Cienc. 2016;88(2):923-32.
[102] Huang CY, Cheng WF, Lee CN, Su YN, Chien SC, Tzeng YL, et al. Serum mesothelin in epithelial ovarian carcinoma: a new screening marker and prognostic factor. Anticancer Res. 2006;26(6C):4721-28.
[103] Hellstrom I, Raycraft J, Kanan S, Sardesai NY, Verch T, Yang Y, et al. Mesothelin variant 1 is released from tumour cells as a diagnostic marker. Cancer Epidemiol Biomarkers Prev. 2006;15(5):1014-20.
[104] Hellstrom I, Hellstrom KE. Two novel biomarkers, mesothelin and HE4, for diagnosis of ovarian carcinoma. Expert Opin Med Diagn. 2011;5(3):227-40.
[105] Imashimizu K, Shiomi K, Maeda M, Aoki N, Igarashi K, Suzuki F, et al. Feasibility of large-scale screening using N-ERC/mesothelin levels in the blood for the early diagnosis of malignant mesothelioma. Exp Ther Med. 2011;2(3):409-11.
[106] Hassan R, Remaley AT, Sampson ML, Zhang J, Cox DD, Pingpank J, et al. Detection and quantitation of serum mesothelin, a tumour marker for patients with mesothelioma and ovarian cancer. Clin Cancer Res. 2006;12(2):447-53.
[107] Greaves P, Gribben JG. The role of B7 family molecules in hematologic malignancy. Blood. 2013;121(5):734-44.
[108] Dong Q, Ma X. B7-H4 expression is associated with tumour progression and prognosis in patients with osteosarcoma. Biomed Res Int. 2015;2015:156432.
[109] Sica GL, Choi IH, Zhu G, Tamada K, Wang SD, Tamura H, et al. B7-H4, a molecule of the B7 family, negatively regulates T cell immunity. Immunity. 2003;18(6):849-61.
[110] Xu M, Zhang B, Zhang M, Liu Y, Yin FL, Liu X, et al. Clinical relevance of expression of B7-H1 and B7-H4 in ovarian cancer. Oncol Lett. 2016;11(4):2815-19.
[111] Mao Y, Li W, Chen K, Xie Y, Liu Q, Yao M, et al. B7-H1 and B7-H3 are independent predictors of poor prognosis in patients with non-small cell lung cancer. Oncotarget. 2015;6(5):3452-61.
[112] Zhao LW, Li C, Zhang RL, Xue HG, Zhang FX, Zhang F, et al. B7-H1 and B7-H4 expression in colorectal carcinoma: correlation with tumour FOXP3(+) regulatory T-cell infiltration. Acta Histochem. 2014;116(7):1163-68.
[113] Salceda S, Tang T, Kmet M, Munteanu A, Ghosh M, Macina R, et al. The immunomodulatory protein B7-H4 is overexpressed in breast and ovarian cancers and promotes epithelial cell transformation. Exp Cell Res. 2005;306(1):128-41.
[114] Zhang LL, Shao SL, Wu Y. Expressions of osteopontin and B7-H4 in epithelial ovarian neoplasm and their significance. Chin J Cancer. 2010;29(1):25-29.
[115] Li ZY, Zhang XH, Chen Y, Guo JG, Sai K, Yang QY, et al. Clinical significance of B7-H4 expression in matched non-small cell lung cancer brain metastases and primary tumours. Onco Targets Ther. 2013;6:869-75.
[116] Chen Y, Sun J, Zhao H, Zhu D, Zhi Q, Song S, et al. The coexpression and clinical significance of costimulatory molecules B7-H1, B7-H3, and B7-H4 in human pancreatic cancer. Onco Targets Ther. 2014;7:1465-72.
[117] Arigami T, Uenosono Y, Ishigami S, Hagihara T, Haraguchi N, Natsugoe S. Clinical significance of the B7-H4 coregulatory molecule as a novel prognostic marker in gastric cancer. World J Surg. 2011;35(9):2051-57.
[118] Fan M, Zhuang Q, Chen Y, Ding T, Yao H, Chen L, et al. B7-H4 expression is correlated with tumour progression and clinical outcome in urothelial cell carcinoma. Int J Clin Exp Pathol. 2014;7(10):6768-75.
[119] Wang X, Wang T, Xu M, Xiao L, Luo Y, Huang W, et al. B7-H4 overexpression impairs the immune response of T cells in human cervical carcinomas. Hum Immunol. 2014;75(12):1203-09.
[120] Simon I, Katsaros D, Rigault de la Longrais I, Massobrio M, Scorilas A, Kim NW, et al. B7-H4 is over-expressed in early-stage ovarian cancer and is independent of CA125 expression. Gynaecol Oncol. 2007;106(2):334-41.
[121] Li YY, Zhang WC, Zhang JL, Zheng CJ, Zhu H, Yu HM, et al. Plasma levels of lysophosphatidic acid in ovarian cancer versus controls: a meta-analysis. Lipids Health Dis. 2015;14:72.
[122] Wang FQ, Ariztia EV, Boyd LR, Horton FR, Smicun Y, Hetherington JA, et al. Lysophosphatidic acid (LPA) effects on endometrial carcinoma in vitro proliferation, invasion, and matrix metalloproteinase activity. Gynaecol Oncol. 2010;117(1):88-95.
[123] Aoki J. Mechanisms of lysophosphatidic acid production. Semin Cell Dev Biol. 2004;15(5):477-89.
[124] Luquain C, Singh A, Wang L, Natarajan V, Morris AJ. Role of phospholipase D in agonist-stimulated lysophosphatidic acid synthesis by ovarian cancer cells. J Lipid Res. 2003;44(10):1963-75.
[125] Sedláková I, Vávrová J, Tošner J, Hanousek L. Lysophosphatidic acid (LPA)-a perspective marker in ovarian cancer. Tumour Biol. 2011;32(2):311-16.
[126] Ding F, Niu B. Clinical significance of detecting lysophosphatidic acid and vascular endothelial growth factor in patients with epithelial ovarian carcinoma. Practical J Med Pharmacy. 2013;30:775–77.
[127] Tamir A, Gangadharan A, Balwani S, Tanaka T, Patel U, Hassan A, et al. The serine protease prostasin (PRSS8) is a potential biomarker for early detection of ovarian cancer. J Ovarian Res. 2016;9:20.
[128] Planès C, Randrianarison NH, Charles RP, Frateschi S, Cluzeaud F, Vuagniaux G, et al. ENaC-mediated alveolar fluid clearance and lung fluid balance depend on the channel-activating protease 1. EMBO Mol Med. 2010;2(1):26-37.
[129] Vuagniaux G, Vallet V, Jaeger NF, Hummler E, Rossier BC. Synergistic activation of ENaC by three membrane-bound channel-activating serine proteases (mCAP1, mCAP2, and mCAP3) and serum- and glucocorticoid-regulated kinase (Sgk1) in Xenopus Oocytes. J Gen Physiol. 2002;120(2):191-201.
[130] Yan BX, Ma JX, Zhang J, Guo Y, Mueller MD, Remick SC, et al. Prostasin may contribute to chemoresistance, repress cancer cells in ovarian cancer, and is involved in the signaling pathways of CASP/PAK2-p34/actin. Cell Death Dis. 2014;5:e995.
[131] Selzer-Plon J, Bornholdt J, Friis S, Bisgaard HC, Lothe IM, Tveit KM, et al. Expression of prostasin and its inhibitors during colorectal cancer carcinogenesis. BMC Cancer. 2009;9:201.
[132] Costa FP, Batista EL Jr, Zelmanowicz A, Svedman C, Devenz G, Alves S, et al. Prostasin, a potential tumour marker in ovarian cancer--a pilot study. Clinics (Sao Paulo). 2009;64(7):641-44.
[133] Mok SC, Chao J, Skates S, Wong K, Yiu GK, Muto MG, et al. Prostasin, a potential serum marker for ovarian cancer: identification through microarray technology. J Natl Cancer Inst. 2001;93(19):1458-64.
[134] Xu FJ, Ramakrishnan S, Daly L, Soper JT, Berchuck A, Clarke-Pearson D, et al. Increased serum levels of macrophage colony-stimulating factor in ovarian cancer. Am J Obstet Gynaecol. 1991;165(5 Pt 1):1356-62.
[135] Będkowska GE, Ławicki S, Gacuta E, Pawłowski P, Szmitkowski M. M-CSF in a new biomarker panel with HE4 and CA 125 in the diagnostics of epithelial ovarian cancer patients. J Ovarian Res. 2015;8:27.
[136] Ławicki S, Będkowska GE, Wojtukiewicz M, Szmitkowski M. Hematopoietic cytokines as tumour markers in breast malignancies. A multivariate analysis with ROC curve in breast cancer patients. Adv Med Sci. 2013;58(2):207-15.
[137] Bahar B, Acedil Ayc Iota B, Çoşkun U, Büyükberber S, Benekli M, Yildiz R. Granulocyte colony stimulating factor (G-CSF) and macrophage colony stimulating factor (M-CSF) as potential tumour markers in non small cell lung cancer diagnosis. Asian Pac J Cancer Prev. 2010;11(3):709-12.
[138] Vasiliades G, Kopanakis N, Vasiloglou M, Zografos G, Margaris H, Masselou K, et al. Role of the hematopoietic cytokines SCF, IL-3, GM-CSF and M-CSF in the diagnosis of pancreatic and ampullary cancer. Int J Biol Markers. 2012;27(3):e186-94.
[139] Kirma N, Hammes LS, Liu YG, Nair HB, Valente PT, Kumar S, et al. Elevated expression of the oncogene c-fms and its ligand, the macrophage colony-stimulating factor-1, in cervical cancer and the role of transforming growth factor-beta1 in inducing c-fms expression. Cancer Res. 2007;67(5):1918-26.
[140] van Haaften-Day C, Shen Y, Xu F, Yu Y, Berchuck A, Havrilesky LJ, et al. OVX1, macrophage-colony stimulating factor, and CA-125-II as tumour markers for epithelial ovarian carcinoma: a critical appraisal. Cancer. 2001;92(11):2837-44.

[141] Baiocchi G, Kavanagh JJ, Talpaz M, Wharton JT, Gutterman JU, Kurzrock R. Expression of the macrophage colony-stimulating factor and its receptor in gynaecologic malignancies. Cancer. 1991;67(4):990-96.
[142] Suzuki M, Kobayashi H, Ohwada M, Terao T, Sato I. Macrophage colony-stimulating factor as a marker for malignant germ cell tumours of the ovary. Gynaecol Oncol. 1998;68(1):35-37.
[143] Ueland FR, Desimone CP, Seamon LG, Miller RA, Goodrich S, Podzielinski I, et al. Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumours. Obstet Gynaecol. 2011;117(6):1289-97.
[144] Ueland FR. A Perspective on ovarian cancer biomarkers: past, present and yet-to-come. Kjaer A, ed. Diagnostics (Basel). 2017;7(1):14.
[145] Zhang Z, Chan DW. The road from discovery to clinical diagnostics: lessons learned from the first FDA-cleared in vitro diagnostic multivariate index assay of proteomic biomarkers. Cancer Epidemiol Biomarkers Prev. 2010;19(12):2995-99.
[146] Nowak M, Janas Ł, Stachowiak G, Stetkiewicz T, Wilczyński JR. Current clinical application of serum biomarkers to detect ovarian cancer. Prz Menopauzalny. 2015;14(4):254-59.
[147] Coleman RL, Herzog TJ, Chan DW, Munroe DG, Pappas TC, Smith A, et al. Validation of a second-generation multivariate index assay for malignancy risk of adnexal masses. Am J Obstet Gynaecol. 2016;215(1):82.e1-82.e11.

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