The latest reports on biomarkers used in the diagnosis of ovarian cancer

Najnowsze doniesienia na temat biomarkerów wykorzystywanych w diagnostyce raka jajnika

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Abstract

Introduction: Ovarian cancer ranks seventh in terms of incidence and eighth in terms of mortality among women worldwide. It is divided into several subtypes. The epithelial type of ovarian cancer is responsible for 90% of cases. The clinical picture is usually an appendage tumor detected by palpation or during pelvic imaging. Symptoms are usually non-specific such as abdominal pushing or bloating.

State of knowledge: Ovarian cancer is usually detected at an advanced stage due to the long duration of absence of symptoms. Therefore, there is an urgent need to look at existing and identify potential biomarkers that can lead to the development of new and more effective predictors for the diagnosis and prognosis of ovarian cancer. The ability of these biomarkers to predict the existence and stages of ovarian cancer could improve early diagnosis and survival of ovarian cancer patients. Currently, the biomarkers CA-125 and HE4 play the most important role in diagnosis. However, there are an increasing number of reports on other biomarkers such as kallikreins, bikunin, VEGF, and mesothelin.

Summary: Partly due to the lack of effective screening, ovarian cancer is usually diagnosed in the final stages. This is why ongoing research into new biomarkers that could contribute to faster detection of the disease is so important. They would also increase the effectiveness of the therapies used and enable a better prognosis of the course of the disease.

Keywords: biomarkers, ovarian cancer, advance

Introduction

Ovarian cancer (OC) ranks seventh in terms of incidence and eighth in terms of mortality among women worldwide. The incidence with which it occurs varies by country and ethnicity. The highest incidence is found among Caucasian, Hispanic, African-American and Asian women [1]. Other determinants such as poverty and poor access to healthcare also affect mortality [2]. It is also noteworthy that there is currently no screening programme to detect ovarian cancer in time [3].

Ovarian cancer is divided into several subtypes. The epithelial type is responsible for 90% of cases. Among this subtype, 97% are non-mucous and 3% are mucinous. Mucinous tumors can be divided by histology int a serous endometrial, clear cell and indeterminate carcinoma [1, 2].

The stage of ovarian cancer is assessed using the 2014 International Federation of Gynecology and Obstetrics (FIGO) classification. It defines four stages of progression [4]. Patients in stages I and II have a 5-year survival rate of 76% to 91%. Unfortunately, the majority of patients are diagnosed at an advanced stage with a 5-year survival of only 30% of patients [5].

Stage	Characteristics
I	Tumor limited to the ovaries
II	Tumor involves one or both ovaries with pelvic involvement
III	Tumor involves one or both ovaries with peritoneal metastases outsider the pelvis or retroperitoneal lymphadenopathy
IV	Distant metastasis including liver parenchyma

Table 1 shows FIGO staging of the ovarian cancer

The best-known risk factor for ovarian cancer is carrying mutations in the BRCA1 and BRCA2 genes. Approximately 10-15% of all ovarian cancers have a genetic basis related to these mutations [6]. Another genetic cause is Lynch Syndrome caused by MMR (mismatch repair) gene mutations. This syndrome is associated with non-polypoid colorectal cancer, which can coexist with other cancers such as ovarian cancer, endometrial cancer or urinary tract cancers [4]. A predisposing factor for the development of ovarian cancer may also be a higher number of ovulatory cycles, which increases the frequency of cell divisions which may lead to the development of a malignant tumour [7]. Studies show that OC is primarily a postmenopausal disease. The median age of diagnosis is 50-79 years [1]. Other risk factors are shown in Figure 1 [4].

The clinical picture is usually an appendage tumour detected by palpation or pelvic imaging. Symptoms are usually non-specific such as abdominal pushing or bloating, urinary symptoms (pushing or increased frequency of urination), abdominal girth enlargement associated with ascites, premature satiety, non-specific abdominal and pelvic pain [4, 8, 9].

Figure 1 shows risk factors for the ovarian cancer.

State of knowledge

A biomarker is any substance or structure that can be measured in the body or its products. They allow the study of changes associated with a physiological state such as pregnancy and the prediction of the occurrence or detection of the presence of diseases, thereby influencing the course and outcome of patient treatment. They can also be used as specific measures of the effectiveness of the use of a specific medicinal product in therapy [10].

Ovarian cancer is usually detected at an advanced stage due to the long duration of absence of symptoms. Therefore, there is an urgent need to look at existing and identify potential biomarkers that can lead to the development of new and more effective predictors for the diagnosis and prognosis of ovarian cancer. The ability of these biomarkers to predict the existence, stages and associated therapeutic efficacy of ovarian cancer would enable improved early diagnosis and survival of ovarian cancer patients [11].

CA-125

CA-125 also known as Mucin-16 is a high molecular weight glycoprotein encoded by the MUC-16 gene [12]. It is the most commonly used tumor marker in ovarian cancer and was first identified in 1981 by Bast, Knapp et al [13].

The upper limit for CA-125 is 35 U/ml. A study by Chen et al. showed that the initial CA-125 level was higher in patients with type II ovarian cancer, which has a worse prognosis. It is worth noting that the biomarker alone can not determine the type of cancer [14]. CA-125 levels are often measured in women with ovarian cysts to rule out malignancy.

In recent years, however, a high number of false-positive results have been observed due to elevated levels of this marker in patients with adenocarcinoma [15]. An important drawback in the use of CA-125 is that its elevated levels are observed in different physiological and pathological states such as menstruation, pregnancy, endometriosis or peritonitis [16]. A meta-analysis by Hirsch et al. suggest that this marker could be useful for the diagnosis of endometriosis [17]. Another study showed that CA-125 levels were significantly higher in patients with endometriotic cysts compared to patients with other benign ovarian tumours [14].

Findings suggest that smoking does not cause changes in serum CA-125 levels [18]. In contrast, its levels may change during menstrual cycles. Binary contraception and a high BMI are unlikely to modify levels of this marker [19, 20].

An important aspect is the correlation between CA-125 levels and response to treatment in patients with ovarian cancer. Results show that the higher its level, the less likely it is to achieve optimal cytoreduction [21]. A study by Vorgias et al. showed that levels above 500 IU/ml are associated with more radical surgery and poorer outcomes [22]. With the results of the Arab et al. study, a model was created to predict optimal surgical outcome, which was based on the fact that patients with a CA-125 value of 420 IU/ml or less, without massive ascites and liver metastases were more likely to achieve optimal cytoreduction [23].

HE4

HE4 is human epididymal protein 4, which is a glycoprotein belonging to the four-sulphur whey protein family [24]. This biomarker is mainly expressed in reproductive and respiratory tracts, but its overexpression is also found in ovarian tumours, especially in endometrial and serous subtypes [25]. It may regulate tumour cell adhesion, migration and growth through activation of the EGFR/MAPK signalling pathway [26].

When comparing HE4 to CA-125, it appears that this marker is able to predict OC recurrence before CA-125 in some patients. Laskshmann et al. showed that HE4 has the same sensitivity but higher specificity than serum CA-125 when detecting recurrence [27]. A study by Liao et al. showed positive HE4 values in the urine of some patients even before relapse with normal HE4 and serum CA-125 levels [28].

HE4 levels are stable in patients with endometriosis in contrast to CA-125 [29]. A 2012 study confirmed that this protein is a better diagnostic biomarker in patients with ovarian cancer and endometriosis [30]. Studies show that same as with CA-125, the BMI value is unlikely to modify HE4 concentrations [31]. Smoking, on the other hand, may significantly affect the results of the study as HE4 levels increase from 20 to 30 per cent in smokers compared to non-smokers [32]. Contraception also contributes to differences in HE4 concentrations. Studies have observed that patients using oral contraceptives had lower levels of this marker than patients using other methods of contraception [33].

Kallikreins

Kalikreins are a group of peptidases that are part of a family of proteolytic enzymes belonging to the serine proteases. There are more than 15 kallikrein variants.

In recent decades, numerous studies have shown abnormal expression of KLK family members in ovarian cancer. In particular, elevated expression of KLK 4, 5, 6, 7, 10 and 15 correlates with unfavourable prognosis and late-stage disease [34].

KLK 5-7 expression in type II ovarian cancer tissues was associated with poorer surgical success and higher malignancy grade. These associations suggest the potential of kallikreins as alternative biomarkers for this cancer [35, 36]. Studies by Shih have shown that KLK 6, 8, and 10 re more specific than KLK 4, 5, 11, 14, and 15 in metrial ovarian cancer when differentiating between benign and other malignant secretions in ascites and pleural effusion fluid [37]. Studies show that KLK 7 levels are significantly higher in the two types of ovarian cancer-serous and endometrial. This has been associated with worse FPS in patients [38]. In addition, KLK7 overexpression has been found to induce chemo-resistance and increase levels of alpha5/beta1 integrins, which induce ovarian cell invasion thereby increasing spread to the peritoneum and reinvasion [39]. Another pathway through which KLK7 can stimulate tumour cell invasion and metastasis formation is through cleavage of extracellular matrix (ECM) proteins. Thus, the differential expression of kallikreins shows potential as a diagnostic biomarker for serous and endometrial ovarian cancer, and may indicate a critical role for these peptidases in the ovarian cancer microenvironment contributing to disease progression, chemo-resistance and metastasis formation [40].

Bikunin

Bikunin is a member of the kunin family of serine protease inhibitors. It shows inhibitory activity against trypsin, plasmin and leukocyte elastase. A study by Tanaka et al. showed a correlation between low bikunin mRNA expression and poor prognosis in ovarian cancer patients. The prognostic value of reduced bikunin mRNA expression corresponds to the value of periaortic lymph node metastasis and is independent of typical clinicopathological parameters. The results of the study suggest that loss of bicunin may lead to a more aggressive disease course and a shorter survival time. These data suggest that measuring bikunin mRNA expression in ovarian cancer patients may be a prognostic indicator [41].

VEGF

Vascular endothelial growth factor (VEGF) is a signal protein produced by many cells that stimulates the formation of blood vessels. It is produced by many cell types including tumour cells, macrophages platelets and renal mesangial cells. VEGF also plays a role in normal physiological functions such as bone formation, haematopoiesis and wound healing [42]. The VEGF gene family consists of seven members VEGF-A to VEGF-F [43].

Findings suggest an important role for VEGF-A in the pathogenesis of ovarian cancer, in both limited and metastatic forms of the tumour [44]. It was shown that patients with ovarian cancer had markedly higher levels of VEGF compared to patients with benign ovarian tumours [45]. The ability of VEGF-A to increase microvascular permeability and stimulate tumour growth play a clinical role in tumour biology. Tumours cannot reach large sizes without their own blood supply [46]. VEGF-A appears to be a promising angiogenic marker in serous ovarian cancer. Expression of this factor was higher in metastatic tumours, while low expression in primary tumours was associated with a worse prognosis [47].

A study by Orre et al. showed that vascular density in malignant ovarian tumours is significantly higher than in borderline tumours. In clear cell ovarian cancer, VEGF expression was correlated with vessel density [48].

Nishida et al. found that high VEGF-C expression in the tumour reflects the spread of ovarian cancer and poor prognosis [49]. Yokoyama et al. found that VEGF-D expression showed correlations with poor OS in ovarian cancer [50]. In contrast, Shen et al. showed better OS among patients with ovarian tumours with low VEGF expression [51].

VEGF-C has been shown to lead to increased metastasis of tumour cells to lymph nodes, but also to distant organs [52]. A study by Ding et al. indicated a significant association between serum VEGF-C levels and patient response to bevacizumab therapy. A twofold increase in serum VEGF-C levels at the time of surgery increased the probability of a successful response to bevacizumab therapy by 2.79 times [53].

Mesothelin

Mesothelin (MSLN) is a surface glycoprotein anchored to glycosylphosphatidylinositol (GPI) encoded by the MSLN gene, which is located on chromosome 16p.13.3 [54]. It is normally restricted to pleural, pericardial, peritoneal and vaginal sheath mesothelial cells, but is increasingly being studied in many solid tumours, including ovarian cancer. Mesothelin has biological characteristics that make it a good candidate for use in cancer diagnosis. It is well internalised which makes it a good target for immunotoxins [55]. In addition, it is actively cleared from the cell surface which contributes to the generation of an antigen pool in the ascites or blood which, in turn, allows quantitative assessment of circulating MSLNs [56].

Findings suggest that MSLN expression is associated with more advanced cancer stage and poorer overall survival (OS). In a study by Cheng et al, MSLN was shown to facilitate migration and increase invasiveness of ovarian cancer cells. Its overexpression was a poor prognostic factor for progression-free survival (PFS) and OS of ovarian cancer patients [57].

Mesothelin was detected in various histological types of OC, and was particularly common in the serous subtype [58]. In one study, a splicing variant of soluble mesothelin was named soluble megakaryocyte enhancer factor (SMRP). It was shown that its higher expression was present in patients with serous ovarian cancer compared to those with benign ovarian tumours. Furthermore, SMRP levels were observed to be associated with higher tumour stage according to the International Federation of Gynaecology and Obstetrics (FIGO). These findings suggest that high serum mesothelin levels may indicate lower survival and tumour progression [59].

In addition to blood, mesothelin can also be detected in urine Badgwell et al. showed that MSLN has a higher sensitivity in early-stage ovarian cancer in urine samples than in serum [60]. In a study by Hollevoet, it was observed that urinary mesothelin levels were dependent on impaired glomerular and renal tubular function which may affect the interpretation of mesothelin measurements and contribute to false positives [61]. Studies have also shown that MSLN can trigger chemo-resistance. Its expression in patients with chemosensitive OC was significantly lower than in patients in the chemo-resistant group [57]. In addition, mesothelin reduces paclitaxel-induced cell death through induction of the 3-phosphoinositide kinase PI3K/AKT and MAPK/ERK pathways [62].

Summary

Although many genetic studies have been carried out to date, there is still no clear set of specific genes involved in ovarian carcinogenesis that can be used as a reference standard for cancer detection. Partly due to the lack of effective screening, ovarian cancer is usually diagnosed in the final stages. This is why ongoing research into new biomarkers that could contribute to faster detection of the disease is so important. They would also increase the effectiveness of the therapies used and enable a better prognosis of the course of the disease.

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