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Ovarian Cancer: Diagnostic Biomarkers and Their Significance-An Updated Review

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Abstract:

Background: Ovarian cancer (OC) remains one of the deadliest gynecological cancers, with a significant number of cases diagnosed at advanced stages, resulting in poor survival outcomes. Early detection remains a critical challenge, as conventional methods, including traditional chemotherapy, are often ineffective for late-stage diagnoses. Given that less than 20% of cases are identified at an early stage, the search for reliable diagnostic biomarkers is crucial. This review provides an updated analysis of biomarkers relevant for ovarian cancer diagnosis, emphasizing their significance and clinical utility.

Aim: The aim of this review is to update the current understanding of ovarian cancer biomarkers, specifically focusing on CA-125 and HE4, their diagnostic roles, and their potential to improve early detection, prognosis, and treatment response monitoring.

Methods: This review synthesizes findings from recent studies on ovarian cancer biomarkers, specifically CA-125 and HE4. A detailed analysis of their diagnostic efficacy, sensitivity, specificity, and limitations was conducted. A meta-analysis of studies involving HE4 and CA-125 was included to evaluate their potential in detecting ovarian cancer.

Results: CA-125, the most widely used biomarker, has limitations in specificity, often yielding false positives in benign conditions. Despite its clinical utility in tracking disease progression, its role in early detection is limited. HE4, on the other hand, has shown higher specificity and sensitivity, especially in distinguishing

between different types of ovarian tumors. The combination of CA-125 and HE4, used together in algorithms like ROMA, enhances diagnostic accuracy. Studies show that these biomarkers, particularly in advanced stages, provide valuable prognostic information.

Conclusion: Both CA-125 and HE4 show promise in enhancing ovarian cancer diagnosis, with HE4 offering a more specific and sensitive approach. When used in combination, these biomarkers significantly improve the likelihood of early detection, offering hope for better outcomes. Further research into other biomarkers and improved detection methodologies is essential for advancing ovarian cancer diagnosis and patient survival rates.

Keywords: Ovarian cancer, biomarkers, CA-125, HE4, early detection, diagnosis, prognosis, epithelial ovarian cancer (EOC), cancer screening.

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Introduction:

In 2020, there were 606,520 cancer-related deaths and 1,806,590 newly diagnosed cancer cases in the US. With an estimated 21,750 new cases and 13,940 related deaths in the same year, ovarian cancer (OC) became the most common cause of death among cancers of the female reproductive system. Postmenopausal women are especially vulnerable to OC because the risk of reaching an advanced stage of the disease increases with age. The main causes of this increased risk are the lack of trustworthy early detection techniques and the poor effectiveness of traditional chemotherapy [1]. It is estimated that 1 in 2,500 postmenopausal women have OC [2]. Only 30% of ovarian malignancies survive for five years after being detected, with 70% of cases occurring at advanced stages. On the other hand, a five-year survival rate of over 90% can be achieved with an early identification of OC limited to the ovaries. Even though the survival rate has slightly increased over the last 25 years, a better comprehension of the molecular mechanisms behind OC is still crucial. Given that less than 20% of OCs are identified at a localized stage, new biomarkers have the potential to aid in early diagnosis [3]. The deadliest types of ovarian cancer are epithelial ovarian cancers (EOCs), which are malignant epithelial tumors (carcinomas) among gynecological malignancies. Currently, just the form of the tumor cells is used to classify ovarian epithelial cancers. Six to nine occurrences of these malignancies occur for every 100,000 women worldwide [4]. Depending on the kind of ovarian cells involved, ovarian tumors can be roughly divided into three main kinds. Surface epithelial cells, which cover the ovary and are classified into many subtypes, fall under the first category. Germ cells, the progenitors of ova, make up the second category. Related OC subtypes include dysgerminomas, immature teratomas, and yolk sac tumors. The third group consists of sex cord-stromal cells, which can develop into cancers like Sertoli-Leydig cells and malignant granulosa cells [5,6].

High-grade serous, endometrioid, clear cell, mucinous, and low-grade serous carcinomas are the five subtypes of epithelial ovarian malignancies (EOCs) that are distinguished by their histology and molecular genetic changes. Over 95 percent of all OC cases are EOCs. Based on traits like the degree of cellular proliferation, nuclear atypia, and stromal invasion, these tumors are further classified as benign, borderline (intermediate), and malignant (carcinoma). The nature and clinical behavior of the tumor are better understood thanks to this complex classification scheme [7,8,9]. Based on clinical, genetic, and developmental traits, these histopathological subtypes are incorporated into two primary categories—type I and type II—in the dualistic model of ovarian carcinogenesis. The bulk of instances (about 70%) are type II tumors, while type I ovarian carcinomas make up about 30% of cases. Only 10% of ovarian cancer-related deaths are caused by type I tumors, which are usually limited to the ovaries (stage I) and have a generally better prognosis. These tumors comprise low-grade subgroups such clear-cell, serous, mucinous, and endometrioid tumors, with sporadic occurrences of seromucinous and Brenner tumors. They also behave in a clinically less aggressive manner. Type II tumors, on the other hand, are more aggressive, frequently discovered at advanced stages (III and IV), and have little hope of recovery. A worse prognosis and worse clinical results are linked to type II tumors, which include high-grade undifferentiated, endometrioid, serous, and malignant mixed mesodermal tumors. Remarkably, around 90% of deaths from ovarian cancer

are caused by type II tumors. In order to greatly enhance patient outcomes, some experts advise focusing screening efforts solely on type II cancers [10,11,12,13,14]. The collection of disorders known as ovarian cancer is diverse and complex, with significant variation in both shape and biological function. Despite having a lower prevalence than breast cancer, OC has a disproportionately large impact and is responsible for a sizable number of deaths. Because over 75% of patients have recurrence after surgery and chemotherapy, advanced (stage III) ovarian cancers are very deadly. OC is the fifth most common cause of cancer-related deaths among women in the Western world and the most deadly gynecological cancer worldwide [8,9,15]. Improving screening techniques' effectiveness, especially by identifying certain biomarkers, may significantly raise the possibility of early OC detection.

Tumor Markers in Ovarian Cancer

Because they provide quantifiable traits linked to specific cell types, biomarkers—also known as oncomarkers—are essential to cancer research and treatment approaches. Genes, proteins, and other molecular characteristics are examples of these molecular signatures, which act as impartial medical markers. Evaluating the probability of disease progression or the existence of pathogenic processes is the first of biomarkers' two main purposes. The second is determining how well treatment measures work. During cancer screening, diagnosis, and treatment monitoring, cancer biomarkers—molecules produced by cancerous cells or nearby cells in their microenvironment—can be measured in body fluids including blood and urine. Antigens, cytoplasmic proteins, enzymes, hormones, receptors, oncogenes, and their derivatives are a few examples of these biomarkers [16,17]. High sensitivity and specificity for a certain tumor type, patient acceptability, positive and negative predictive values for prognostic and predictive advantages, and clinical validation through prospective trials are all characteristics of an excellent biomarker. However, none of these ideal conditions are yet met by a single biomarker. Biomarkers are categorized based on their use, such as screening, prognosis, tumor presence or absence detection, and identifying molecular targets for new treatments [18,19]. Utilizing noninvasive and minimally invasive methods to analyze bodily fluids like blood, serum, and plasma, as well as saliva and urine, improves the search for tumor biomarkers. Urine is currently receiving special attention since it is a valuable waste product that is readily available, has a higher volume, and a simpler proteome than blood [20,21,22,23]. The identification and monitoring of ovarian cancer (OC) could be greatly improved by these urine-based biomarkers, which would increase the likelihood of a diagnosis and enable better disease management [17].

CA-125

CA125, first reported in 1981, is a glycoprotein produced by the mucin 16 (MUC16) gene, which can be detected using OC 125 monoclonal antibodies in cancerous ovarian tissues. The normal upper limit for CA125 is set at 35.0 U/mL for both premenopausal and postmenopausal individuals [24].

Role of CA-125 in Diagnosis and Prediction

CA125 is acknowledged by the Food and Drug Administration (FDA) as a useful biomarker for tracking patients with ovarian cancer and assessing treatment responses. Clinical decision-making is aided by the correlation between CA125 levels and survival outcomes as well as the clinical stage. However, because CA125 can be released by non-tumor cells in an inflammatory milieu, its levels alone might not be an appropriate indicator of tumor burden [25]. An increased CA125 level (>35 U/mL) following surgery is suggestive of more malignant tumors, decreased sensitivity to treatment, and persistent illness. Based on CA125 values, the Gynecologic Cancer Intergroup (GCIG) has developed criteria to evaluate tumor remission and recurrence. In particular, a response is defined as a continuous 50% drop in CA125 levels over four weeks, and complete responders are defined as those whose CA125 levels fall within the normal range (<35 U/mL). A twofold increase in CA125 levels over a one-week period indicates the progression or recurrence of the disease. It's crucial to remember that consistently normal CA125 readings do not rule out the likelihood of recurrence or residual disease [26,27]. In women with advanced ovarian cancer, CA125 has emerged as a significant predictive indicator for evaluating treatment results after chemotherapy. The prognosis depends on the measurement of CA125 levels following the first treatment cycle and their

subsequent normalization to less than 35 U/mL by the third cycle. Longer progression-free survival and a positive treatment response are linked to lower CA125 levels and faster normalization. Regular monitoring of CA125 levels during first-line chemotherapy helps identify patients with diminished drug sensitivity, allowing for appropriate treatment regimen changes; a decrease in CA125 levels following neoadjuvant chemotherapy is indicative of a favorable outcome for debulking surgery. CA125 does not seem to have an impact on survival outcomes after chemotherapy, while being an accurate predictor of cancer progression. Moreover, the overproduction of CA125 brought on by insulin signaling exhibits potential as a chemoresistance predictor [28,29,30,31,32,33]. Because patients with CA125 levels below 10 U/mL typically had prolonged progression-free survival (PFS), recent research has emphasized the significance of lowering nadir CA125 levels. It's unclear how maximal surgical efforts may affect these lower ratings [34, 35].

Limitations of CA-125 as a Diagnostic Marker

There are a number of drawbacks to using CA125 levels as the only diagnostic indicator for epithelial ovarian cancer (EOC), chief among them being the possibility of false positives in healthy people and those with benign diseases. While lower CA125 levels are typically linked to earlier cancer stages and better outcomes, about 20% of EOC patients do not have elevated CA125 levels. By attaching to antibodies, circulating immune complexes (CICs) can reduce CA125 quantities, making detection more difficult. To reduce needless diagnostic costs and increase the precision of EOC diagnosis, these parameters need to be carefully considered [25,36,37,38,39]. The Prostate, Lung, Colorectal, and Ovarian (PLCO) and the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) are two important studies that have shown the limits of CA125 as a valid ovarian cancer screening tool. According to the PLCO trial, when compared to standard care, the combination of CA125 screening with ultrasonography did not significantly increase early detection rates or mortality outcomes. Furthermore, 15% of patients experienced serious surgical problems as a result of false-positive CA125 screening results [40,41]. Comparing the CA125 screening group to the control group, the UKCTOCS study also found no discernible mortality advantage [42, 43].

HE4

HE4 is a glycoprotein encoded by the WFDC2 gene, functioning as a serine proteinase inhibitor. It has emerged as a potential biomarker for ovarian cancer (OC), detectable in both blood and urine samples through enzyme immunoassay techniques. HE4 shows overexpression in specific subtypes of OC, notably a 100% occurrence in endometrioid tumors and a 93% incidence in serous OC. This overexpression facilitates its role in distinguishing among different tumor types, contributing significantly to the differential diagnosis process. The U.S. Food and Drug Administration (FDA) approved the use of HE4 in 2008 for monitoring patients already diagnosed with OC, while it cautioned against utilizing this biomarker for the screening of asymptomatic early-stage OC [17,44,45].

Diagnostic Value of HE4

In order to determine how well the preoperative plasma tumor markers HE4 and CA125 predict cancer mortality in women with epithelial ovarian cancer (EOC), a new study was conducted at the University Hospital of Quebec City. Significant correlations between HE4 levels and important prognostic markers were found in the study for both the training and validation groups. When it came to death prediction, HE4 and CA125 performed similarly in the training group, and there was a significant correlation in the validation cohort. Nevertheless, the relationship between HE4 levels and mortality was no longer significant when preoperative prognostic variables were taken into account. In particular, HE4 showed a greater correlation with mortality outcomes in patients of serous ovarian cancer. According to these results, HE4 may provide useful information for predicting death when combined with other prognostic variables, especially for patients with serous ovarian cancer [22].

The diagnostic value of serum HE4 as a biomarker for ovarian cancer was evaluated by a meta-analysis that included 38 trials and 14,745 participants. The results showed promising discriminative

potential with a clinically significant specificity of 0.92 and a sensitivity of 0.79. The serum HE4 showed promise as a diagnostic tool with a significant area under the curve (AUC). Its diagnostic utility in the context of ovarian cancer detection is further supported by the post-test probability for patients who are HE4-positive and HE4-negative [46]. In a different prospective research, 1,229 women with symptoms were studied to determine the effectiveness of HE4 both by itself and in conjunction with CA125. With an AUC of 0.96, the Risk of Ovarian Malignancy Algorithm (ROMA) was determined to have the greatest performance. While ROMA performed best in women over 50, the combination of CA125 and HE4 offered better sensitivity and specificity in women under 50. When compared to CA125, HE4 alone showed greater sensitivity but decreased specificity [47]. The predictive importance of HE4 measures after first-line treatment for women with ovarian cancer was examined in a 2018 study. Platinum sensitivity, overall survival (OS), progression-free survival (PFS), and surgical results were all associated with elevated HE4 levels. According to these results, HE4 may be a useful biomarker for evaluating the effectiveness of treatment and forecasting the course of ovarian cancer [48].

The accuracy of HE4, CA-125, the Risk of Ovarian Malignancy Algorithm (ROMA), and the Risk of Malignancy Index (RMI) in predicting ovarian cancer in patients with pelvic masses was assessed in a different diagnostic comparative research. Serum CA125 levels (CA125), menopausal state (M), and ultrasound score (U) are among the variables that are included in the RMI [50]. The most accurate diagnostic technique overall was ROMA, which was followed by HE4, CA-125, and RMI. When it came to detecting benign tumors, HE4 and ROMA outperformed CA-125 by a significant margin. While HE4 demonstrated the best specificity in postmenopausal women, both HE4 and ROMA demonstrated higher specificity and negative predictive value in premenopausal women. According to these results, HE4 and ROMA might be important diagnostic indicators, particularly when it comes to differentiating benign from malignant masses in particular patient categories [49]. Elevated HE4 levels at diagnosis, after cytoreductive surgery, and during first-line chemotherapy were associated with an increased risk of recurrence, according to a single-center study that included 188 patients with ovarian cancer. Larger residual tumors following primary surgery and individuals who became resistant to platinum-based treatment were specifically linked to higher HE4 levels. Furthermore, when a second recurrence was diagnosed, patients with neoplastic remnants larger than 10 mm had noticeably elevated HE4 levels [51]. Lastly, preoperative blood HE4 levels above 500 pM were substantially associated with lower 5-year overall survival rates (27% versus 59%), according to a retrospective examination of 89 EOC patients. These results highlight HE4's potential as a prognostic marker for predicting treatment response, overall survival outcomes, and ovarian cancer recurrence [52].

Complementary Role of HE4 to CA-125

A multitude of studies have underscored the benefits of employing dual biomarkers in tandem to enhance both specificity and sensitivity when analyzing premenopausal and postmenopausal women with benign ovarian cysts. In a study conducted in 2003, blinded tests were performed on serum samples obtained from 37 ovarian cancer patients (comprising 7 with early-stage and 30 with late-stage cancer), 65 healthy asymptomatic controls, and 19 individuals with benign ovarian conditions. The predominant histology found in the ovarian cancer patients was serous ovarian carcinoma (21 cases), with the most frequent stage being stage III (24 cases). Both CA125 and HE4 displayed limitations in predicting ovarian cancer, as HE4 failed to detect 7 cases and CA125 missed 8 cases when using a specificity threshold of 95% for positivity [53].

In a multicenter prospective study involving 531 patients diagnosed with pelvic masses and scheduled for surgery, preoperative serum levels of HE4 and CA125 were measured to stratify patients into low and high-risk groups for epithelial ovarian cancer (EOC). This study included patients with benign tumors, EOC, low malignant potential (LMP) tumors, non-EOC malignancies, and non-ovarian cancers. The model demonstrated both high specificity and sensitivity across postmenopausal and premenopausal groups, effectively categorizing patients into high and low-risk groups and accurately classifying a substantial number of EOC cases as high-risk [54]. A separate prospective study assessing CA125 and HE4

levels in both blood and ascites samples found that while elevated levels of these markers were identified in baseline samples from patients with advanced high-grade serous EOC, they were not able to distinguish between those with complete resection and those with residual disease. Following surgical treatment, tumor marker levels decreased, likely due to the reduction in ascites volume and the prolonged half-life of CA125. Nevertheless, prior studies have demonstrated that CA125 and HE4 levels, both before and after chemotherapy initiation, could serve as predictive markers for treatment response and survival outcomes [55].

In a prospective multicenter trial conducted by Moore et al., the accuracy of the Risk of Malignancy Index (RMI) and the Risk of Ovarian Malignancy Algorithm (ROMA) in diagnosing EOC was compared. ROMA, which combines HE4 and CA125, exhibited higher sensitivity (94.3% at 75% specificity) than RMI (84.6%) in distinguishing between benign and EOC status. ROMA also demonstrated superior sensitivity in detecting early-stage disease (stage I and II). These results highlight the increased diagnostic utility of ROMA in identifying women with EOC [56]. A prospective study involving CA125, HE4, and ROMA demonstrated substantial differences between benign and malignant ovarian cases, with elevated CA125 levels observed in patients with endometriosis and ovarian fibromas/thecomas. Variations in HE4 levels were noted across different types of cystadenomas, cystadenofibromas, and endometriosis. ROMA was significantly elevated in certain benign masses when compared to endometriosis. However, there were no significant distinctions in CA125, HE4, and ROMA levels between epithelial ovarian cancers (EOC) and metastatic tumors. Furthermore, no significant differences were identified between different FIGO stages, except for a clear distinction between early (FIGO I-II) and advanced (FIGO III-IV) stages [57].

Monitoring EOC patients using serum HE4 levels showed performance parameters comparable to those of CA125. The combination of HE4 and CA125 enhanced the accuracy, sensitivity, and negative predictive value when compared to the use of either marker alone. The study concluded that HE4 is equivalent to CA125 in monitoring EOC patients, with the dual biomarker approach providing enhanced monitoring capabilities [58]. Furthermore, HE4 levels were found to be significantly elevated in patients with ovarian and endometrial cancer when compared to healthy controls, with the highest levels recorded in serous carcinomas. Combining HE4 and CA125 yielded the highest accuracy and sensitivity in distinguishing ovarian cancer patients from both healthy controls and those with ovarian endometriosis [59]. In a prospective study, HE4 was shown to have higher specificity for benign diseases in comparison to CA125, and the combination of HE4 and CA125 exhibited the highest sensitivity for differentiating invasive epithelial ovarian cancers from benign ovarian neoplasms [60]. HE4 was also recognized as the top-performing individual biomarker for distinguishing between benign ovarian tumors and malignancies, including borderline tumors. A combined model that incorporated HE4, CA125, and age demonstrated the highest diagnostic performance [61]. These findings suggest that HE4 is a potentially valuable biomarker for ovarian carcinoma, offering diagnostic capabilities comparable to CA125 in distinguishing women with both localized and advanced ovarian cancer from healthy individuals. Furthermore, HE4 appears superior to CA125 in differentiating patients with malignant ovarian disease from those with benign ovarian conditions, particularly when applied at high specificity.

CA 15-3

In a 1988 investigation, elevated CA 15-3 levels (>30 U/mL) were observed in 41% of cancer patients, particularly among those at advanced stages and in ovarian cancer cases. These elevated levels were associated with the presence of residual tumors, treatment response, and disease progression during chemotherapy [62].

Complementary Role of CA 15-3 to CA-125

Notable differences in tumor marker levels were found between the cancer group and both the benign and healthy control groups, indicating higher levels of these markers in cancer patients. When multiple tumor markers were combined, the sensitivity of the diagnostic approach improved relative to the use of individual markers. Specifically, the combination of CA72-4, CA15-3, and CA125 showed promise as

a diagnostic tool for ovarian cancer [63]. Another study evaluated the use of an Artificial Neural Network (ANN) model for detecting early-stage ovarian cancer by utilizing multiple serum markers. The ANN model displayed improved performance in distinguishing early-stage ovarian cancer patients from healthy individuals, with the composite index generated by the model offering greater diagnostic power than CA125 alone. The use of multiple serum markers through the ANN model enhanced both sensitivity and specificity, demonstrating its potential for improving early detection and diagnosis of ovarian cancer [64].

CA 19-9

CA19-9 is a well-established marker for pancreatic, gastric, and hepatobiliary malignancies, and recent studies have explored its potential use in ovarian cancer screening. Fahmy et al. included CA19-9 among the six biomarkers they investigated, reporting promising findings in terms of high sensitivity and specificity. These results suggest CA19-9's potential to both rule in and rule out ovarian cancer. In a study involving 120 patients with ovarian tumors and carcinoma, as well as 30 healthy controls, levels of miRNA-204, CA125, CA19-9, hepcidin, microfibril-associated glycoprotein 2, and ferroportin were measured. The analysis revealed that miRNA-204, CA125, and CA19-9 levels were elevated in ovarian cancer patients, while hepcidin, microfibril-associated glycoprotein 2, and ferroportin levels were decreased. ROC analysis indicated that both CA125 and CA19-9 exhibited high diagnostic performance individually. Furthermore, the combination of microRNA-204, CA125, and CA19-9 showed the highest diagnostic performance, whereas hepcidin, microfibril-associated glycoprotein 2, and ferroportin demonstrated weaker diagnostic efficacy [65]. In a separate retrospective study, data from 314 patients diagnosed with mucinous ovarian tumors were analyzed. Preoperative serum levels of CA19-9, CA125, and CEA were assessed, and their diagnostic performance was evaluated using receiver operating characteristic curves. The study also examined the relationship between clinicopathological factors and biomarker levels. The results demonstrated that elevated levels of CA19-9, CA125, and CEA, in conjunction with larger tumor size, were correlated with an increased risk of malignancy. Among the three markers, CA125 provided the highest diagnostic performance in distinguishing between benign, borderline, and malignant mucinous ovarian tumors. The preoperative elevation of CA19-9, CA125, and CEA, along with tumor size, emerged as significant predictors in differentiating tumor types [66].

hCG

Human chorionic gonadotropin (hCG) is expressed across a range of tumor types, including ovarian cancer (OC), positioning it as a potential prognostic and therapeutic target. hCG exists in various isoforms within biological fluids, each exhibiting distinct biological activities. These isoforms include intact hCG, cleaved hCGn, free β subunits (hCGβ), inactive hCGα, the β-core fragment, and nicked free β-subunit (hCGβn) [67].

The role of human chorionic gonadotropin (hCG) in epithelial ovarian cancer (EOC) has been explored in two studies. One study found significantly elevated levels of both hCG mRNA and protein expression in EOC cases, with increased expression in advanced-stage EOC samples. Elevated hCG expression, along with tumor metastasis, was identified as an independent unfavorable prognostic factor impacting overall survival [68]. A second study focused on serum hCG levels in ovarian tumor patients and discovered that 68% of ovarian cancer tissues tested positive for hCG, with variations noted across different histological subtypes. The expression of hCG was significantly influenced by tumor grade and stage. Patients with hCG-positive tumors that were LH-R(+)/FSH-R(−) exhibited improved 5-year survival rates [69]. Further investigation into the expression of LH/hCG receptors in ovarian tumors revealed positive expression in a considerable proportion of ovarian cancers, borderline tumors, and benign cystadenomas. LH/hCG receptor-positive tumors were linked to a more favorable prognosis, particularly in well-differentiated cancer phenotypes. These findings underscore the potential of hCG and LH/hCG receptors as viable targets for innovative cancer treatments, aiming to improve therapeutic effectiveness while minimizing side effects [70].

The diagnostic value of human chorionic gonadotropin (hCG) and its subunit β-hCG has been examined in ovarian cancer patients. Vartiainen et al. observed elevated levels of hCGβ in 29% of ovarian cancer patients, with an increasing frequency observed in advanced stages and specific cancer types. Elevated CA125 levels were also noted in 79% of patients, and these levels correlated with cancer stage. Both hCGβ and CA125 demonstrated strong associations with prognosis, although in a multivariate model, only hCGβ, stage, and grade remained significant. A cutoff level of 2 pmol/L for hCGβ effectively differentiated patients based on prognosis, particularly in advanced-stage disease [71]. In a separate study, β-hCG levels in ovarian cancer patients were monitored before and after surgery, revealing significant differences across cancer stages. However, the diagnostic utility of β-hCG was found to be inconsistent, with both false positive and false negative results being observed [72]. Immunohistochemical analysis of ovarian carcinoma tissues revealed increased β-hCG expression in metastatic tumors, with the expression of this marker being associated with unfavorable clinical characteristics such as advanced stage, larger tumor size, poor differentiation, and high-grade serous carcinoma. These findings indicate that β-hCG expression is linked to more aggressive clinical features in ovarian cancer [73].

Inhibin

Inhibins, composed of α and β subunits, are critical growth factors involved in regulating fertility and are predominantly produced by ovarian follicles. Measurement of total inhibin is essential in the context of ovarian cancer investigations, as different tumor subtypes produce varying quantities of inhibin isoforms. Elevated total inhibin levels are notably observed in postmenopausal women with granulosa cell tumors and mucinous epithelial cancers. When combined with CA125, inhibin enhances ovarian cancer detection, especially for certain subtypes. However, inhibin has limited diagnostic utility in premenopausal women [74]. A study evaluating serum inhibin concentrations in postmenopausal women with ovarian cancer using the αC inhibin immunofluorometric assay (IFMA) and CA125 demonstrated improved sensitivity and comparable or superior specificity compared to prior methodologies [75]. In postmenopausal women without ovarian malignancies, inhibin A and B levels are generally undetectable, while the combination of inhibin B and anti-Mullerian hormone (AMH) shows promise for diagnosing and monitoring granulosa cell tumors. Total inhibin, encompassing the free alpha subunit and inhibin A and B, may be beneficial in some cases of serous and mucinous epithelial carcinomas, particularly when used in conjunction with CA-125. Nevertheless, the efficacy of inhibin measurement in premenopausal women and for detecting early-stage tumors remains uncertain [76].

Inhibin is a recognized tumor marker for ovarian granulosa cell tumors (GCTs), with elevated serum levels observed in GCT patients. Assays such as inhibin radioimmunoassay (RIA) and inhibin enzyme-linked immunosorbent assay (ELISA) have been developed, with the latter showing significant potential for broader clinical application. Total inhibin levels are typically low in healthy postmenopausal women but can differentiate ovarian cancer cases effectively. When combined with CA125, inhibin improves detection accuracy, demonstrating high sensitivity and specificity for identifying ovarian cancers [77]. In normal postmenopausal women, inhibin levels are usually undetectable; however, when detectable, they exhibit a dose-response relationship with inhibin A. In early-stage mucinous carcinomas, inhibin levels have been identified, suggesting potential sensitivity for detecting early-stage disease. The precise biological and molecular mechanisms responsible for the elevated inhibin levels in ovarian cancer remain unclear, though elevated gonadotropins are suspected to contribute [78]. Given the propensity of GCTs for metastasis and recurrence, monitoring inhibin B, a biomarker that reflects tumor burden, can be beneficial for evaluating treatment response and detecting disease recurrence [79]. Inhibin, particularly inhibin B, remains a valuable circulating tumor marker for GCTs, and additional research is needed to investigate the molecular pathogenesis of ovarian tumors and the role of inhibin in their development [80].

AFP

Alpha-fetoprotein (AFP) is a fetal serum protein that can serve as a marker for identifying cancerous growths. However, elevated AFP levels in epithelial ovarian carcinoma (EOC) may lead to misdiagnosis, especially in younger women, as high AFP levels are atypical in EOC. This presents challenges

for accurate diagnosis and underscores the importance of careful clinical evaluation. A study investigating AFP-producing EOC found that it was associated with aggressive disease behavior and poor prognosis. AFP expression was confirmed in all cases, suggesting differentiation into yolk sac components. Serum AFP levels are not routinely assessed in older women, which may result in missed diagnoses [81]. Another study assessed multiple tumor markers, including AFP, and determined that these markers effectively differentiated ovarian cancer from benign cases and healthy individuals [82]. AFP-producing ovarian tumors are rare and present significant diagnostic challenges. The rarity and poor prognosis of these AFP-producing tumors highlight the need for enhanced management strategies [83]. Alpha-fetoprotein, in combination with other serum markers, is commonly employed in the monitoring of ovarian germ cell tumors (OGCT), though its utility in early-stage screening is limited. Monitoring AFP and βhCG levels is important for prognosis, and inhibin B is valuable for tracking granulosa-theca cell tumors [84]. A study demonstrated that a combined diagnostic approach incorporating transvaginal sonography, color Doppler, and tumor marker tests offers high diagnostic accuracy for ovarian cancer [85].

LDH

Lactate dehydrogenase (LDH) is an enzyme involved in the glycolytic pathway, responsible for converting pyruvate to lactic acid. Studies have revealed elevated LDH levels in the blood of ovarian cancer patients, indicating its release from neoplastic cells into the surrounding medium. A prospective study found significantly higher serum LDH levels in ovarian cancer patients. Specifically, using a cutoff level of 450 IU/mL for serum LDH, the study observed a sensitivity of 60%, specificity of 86%, positive predictive value of 70%, and negative predictive value of 75%. The authors suggested that serum LDH levels could serve as a reliable biochemical marker to distinguish ovarian cancer from benign tumors [86]. In 2017, Bastani et al. assessed the diagnostic value of various serum markers (prostasin, CA125, LDH, AFP, hCG + β) in epithelial ovarian cancer (EOC) and their ability to differentiate EOC from benign tumors and healthy controls. The findings demonstrated that serum levels of prostasin, LDH, and CA125 were significantly higher in EOC patients compared to individuals with benign tumors and healthy controls. LDH levels were found to increase with the advancement of EOC stages. The combination of prostasin and LDH with CA125 improved the prediction of EOC status. This multi-marker approach holds promise for providing more accurate differential diagnoses in EOC patients [87].

Emerging Tumor Markers:

MicroRNAs:

MicroRNAs (miRNAs) are short RNA molecules that play a pivotal role in the regulation of gene expression, influencing a wide range of biological processes. Initially, miRNA genes are transcribed into primary miRNAs (pri-miRNAs), which are subsequently processed into precursor miRNAs (pre-miRNAs). These pre-miRNAs are then further cleaved in the cytoplasm to generate miRNA duplexes. The mature miRNA regulates gene expression by targeting messenger RNAs (mRNAs) for either cleavage or translational repression, contingent upon the complementarity between the miRNA and mRNA. Dysregulation of miRNA expression is implicated in various human diseases, including cancer [88]. In ovarian cancer (OC), aberrant miRNA expression has emerged as a promising diagnostic and prognostic tool, with circulating miRNAs (cirMiRs) presenting non-invasive biomarkers for the disease [89]. miRNAs regulate the expression of multiple genes, which makes them particularly valuable for understanding the genetic underpinnings of diseases [90,91]. These molecules remain stable in circulation, often bound to chaperone proteins such as Argonaute 2 (Ago2) or encapsulated in extracellular vesicles, providing resistance to degradation by ribonucleases [92,93]. To date, more than 2,500 miRNAs have been identified, each capable of targeting numerous genes within specific pathways, offering critical insights into gene regulation and cellular behavior [90,91,94]. In the context of ovarian cancer, the Let-7 and miR-200 families have been linked to tumor development. The Let-7 family, in particular, has potential utility in selecting chemotherapy regimens, whereas the role of miR-200 in modulating chemoresistance remains an area for further investigation. Despite the promise of miRNAs as predictive biomarkers for chemotherapy responses, additional research is necessary to establish their clinical utility. Circulating plasma/serum

miRNAs offer great potential for early diagnosis of ovarian cancer; however, further validation of these biomarkers is required before their widespread application in clinical settings [94]. Dysregulated miRNAs in OC often function as tumor suppressors or oncogenes. For example, reduced expression of miRNA-processing enzymes has been associated with advanced tumor stages and poorer patient outcomes. The Let-7 and miR-200 families are commonly altered in ovarian cancer, and various miRNAs are currently being explored for their diagnostic and therapeutic potential. Notably, serum miRNA panels hold promise for improving the diagnosis and monitoring of ovarian cancer [10]. In addition, miRNAs such as let-7e, miR-30c, miR-125b, miR-130a, miR-335, miR-340, miR-381, and miR-520f have been linked to chemoresistance in OC, underscoring the intricate role of miRNAs in disease progression and treatment outcomes [95].

MiRNA expression profiles also show diagnostic potential in ovarian cancer, with certain miRNAs being differentially expressed in OC tissues. Circulating miRNAs in blood and urine are emerging as promising diagnostic markers. Moreover, miRNAs correlate with histological subtypes, chemoresistance, and prognosis, providing valuable insights into disease progression and therapeutic response in OC [96]. The altered expression of miRNAs in OC is closely linked to disease stage, response to treatment, and overall survival. Specific miRNAs, such as miR-21, miR-200a, and miR-200c, offer diagnostic and prognostic value, whereas miR-141 and let-7f are associated with poor progression-free survival. Notably, miR-193a functions as a tumor suppressor [89]. A study by Yokoi et al. demonstrated that a panel of eight miRNAs could distinguish early-stage ovarian cancers from benign tumors, achieving sensitivity of 86% and specificity of 83%. This panel was able to detect miRNAs in extracellular vesicles (EVs) isolated from cultured ovarian cancer cell lines, further enhancing its diagnostic applicability [97].

DNA Methylation Patterns

DNA methylation markers present significant potential for the early detection of ovarian cancer (OC), surpassing traditional biomarkers such as CA125 [98,99]. The analysis of cell-free DNA (cfDNA) methylation markers has shown promise in identifying early-stage OC, particularly in patients from the average-risk population, who typically remain asymptomatic in the early stages, leading to incidental diagnoses. As a result, the development of reliable DNA methylation markers for early OC detection remains a critical area of research to improve clinical applicability [100,101]. In cancer biology, frequent genetic alterations include the hypermethylation of tumor suppressor gene promoters and hypomethylation of oncogenes. Methylation-specific polymerase chain reaction (MSP) is a highly sensitive technique capable of detecting even a single methylated allele in a pool of 1,000 unmethylated alleles, making it a valuable tool for identifying DNA methylation alterations as the disease progresses [102,103]. Multiplexed MSP of cfDNA has shown high sensitivity (85%) and specificity (91%) for early-stage ovarian cancer, outperforming CA125 alone as a diagnostic marker [104]. A pioneering study by Widshwender et al. developed a three-DNA-methylation-serum-marker panel using ultra-high coverage bisulfite sequencing. This panel was successful in differentiating high-grade serous ovarian cancer patients from healthy individuals or those with benign pelvic masses, achieving a sensitivity of 41.4% and specificity of 90.7%. When applied to serum samples collected 1–2 years before the diagnosis of ovarian cancer, the panel exhibited a sensitivity of 16.7% and specificity of 96.9% [98].

DNA methylation serves as a valuable marker for analyzing cancer cell fractions, offering time, cost, and independence from allelic status advantages. This method, when combined with other markers, reduces the dependency on pathologists, facilitating more efficient analysis of ovarian cancer cell fractions [105]. Furthermore, a study identified DNA methylation markers such as COL23A1, C2CD4D, and WNT6 that demonstrate high sensitivity and specificity for the detection of early-stage ovarian cancer. These markers exhibit aberrant methylation patterns in early-stage OC and have shown promise in differentiating OC from healthy controls. This panel holds potential as a complementary diagnostic approach, especially for CA125-negative samples [98]. Late-stage methylation markers, however, have limited use in early OC detection, whereas early-stage markers remain stable throughout cancer progression, providing a robust tool for detecting ovarian cancer at all stages [106]. Genes such as SIM1 and ZNF154 have been identified

as potential methylation markers for assessing ovarian cancer cell fractions, with ZNF154 validated as a reliable and cost-effective marker for this purpose [107].

Ovarian clear cell carcinoma (OCCC) can be classified into two distinct clusters based on DNA methylation patterns. Cluster 1, associated with advanced stages, poor outcomes, TP53 mutations, and residual disease, contrasts with Cluster 2, which is characterized by early-stage disease, aneuploidy, ARID1A/PIK3CA mutations, and better overall survival. The molecular and clinical heterogeneity of OCCC is further influenced by immune-related pathways and ARID1A mutations [108]. Ovarian cancer DNA methylation analysis has identified 250 prognosis-related loci, revealing six subtypes with varying patterns and prognoses. Subtype 2, exhibiting the highest methylation levels, is associated with the best prognosis, whereas subtypes 4 and 5, with lower methylation levels, are linked to poorer prognoses. Hypomethylation correlates with worse outcomes, suggesting that these subtypes could serve as biomarkers for personalized treatment and prognosis prediction [109]. A comprehensive study identified 89 CpG sites associated with epithelial ovarian cancer (EOC) risk, including 12 CpG sites and five genes (MAPT, HOXB3, ABHD8, ARHGAP27, and SKAP1) consistently associated with EOC risk. Methylation at these sites may regulate gene expression and impact the risk of serous and high-grade serous ovarian cancer, offering potential targets for personalized treatment strategies [110].

Genes such as HOXA10 and HOXA11 exhibit significant DNA methylation differences in ovarian cancer, with HOXA11 methylation correlating with poor prognosis and residual tumor presence. Conversely, higher HOXA10 methylation levels are found in poorly differentiated cancers. Low HOXA11 methylation is associated with minimal residual tumors, making it an independent prognostic marker. Methylation frequency increases from non-neoplastic tissue to primary ovarian cancer, underscoring the diagnostic and prognostic value of these markers [111]. A comprehensive analysis revealed hypomethylated-upregulated (HOUP) genes associated with ovarian cancer progression, offering potential as prognostic markers, while hypermethylated-downregulated (HEDW) genes were found to be enriched in cancer-related pathways. Dysregulated hub genes and their negative correlations with methylation levels provide further insights into the epigenetic alterations characteristic of ovarian cancer, highlighting the potential of these genes as biomarkers [112].

Cervical scrapings from Pap tests have shown significant hypermethylation in five genes in OC patients. An integrated model using methylation levels demonstrated high sensitivity and specificity in predicting OC risk, offering potential for improved detection of female genital tract malignancies [113]. Additionally, cfDNA methylation analysis has identified specific differentially methylated regions (DMRs) associated with ovarian cancer, further supporting the development of customized methylation panels with distinct OC-specific DMRs. These findings suggest that DNA methylation patterns could serve as both diagnostic and prognostic markers for ovarian cancer [114].

Conclusion:

Ovarian cancer (OC) continues to be a major health concern due to its high mortality rate and the challenge of detecting it at an early, treatable stage. Despite advances in treatment, most ovarian cancer cases are diagnosed at an advanced stage, where the prognosis remains poor. One of the main hurdles in improving survival rates is the lack of effective early diagnostic tools. Traditional methods, such as imaging and surgery, are not ideal for early-stage detection, and chemotherapy's efficacy remains limited in late-stage patients. Biomarkers, such as CA-125 and HE4, have become critical in diagnosing and monitoring ovarian cancer. CA-125, identified decades ago, is still widely used as a diagnostic and prognostic marker. However, its sensitivity and specificity remain a significant issue, with false positives occurring in benign conditions and some cancer patients presenting with normal levels. Despite this, CA-125 is valuable in assessing treatment response and monitoring disease progression, particularly in advanced stages of ovarian cancer. HE4 has emerged as a promising alternative biomarker with greater specificity for ovarian cancer, especially for distinguishing between different types of epithelial ovarian cancers. It has been shown to provide useful prognostic information and could complement CA-125, especially when integrated into algorithms like ROMA (Risk of Ovarian Malignancy Algorithm). The combination of CA-125 and HE4 has

proven to improve diagnostic accuracy, particularly when used to differentiate malignant from benign conditions. Studies have demonstrated that HE4, in conjunction with CA-125, offers significant benefits for early detection, prognosis, and treatment planning, providing healthcare professionals with a reliable tool for improving patient outcomes. Despite these advancements, the current biomarkers still fall short of providing a perfect solution for ovarian cancer detection. Many patients, particularly in the early stages, present without elevated biomarker levels, indicating a need for further research into other potential biomarkers and non-invasive diagnostic technologies. The integration of new biomarker profiles and liquid biopsy technologies may provide the breakthrough needed for earlier and more accurate detection, leading to better survival rates for ovarian cancer patients.

References:

1. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. *CA Cancer J. Clin.* **2020**, *70*, 7–30.
2. Bast, R.C., Jr.; Brewer, M.; Zou, C.; Hernandez, M.A.; Daley, M.; Ozols, R.; Lu, K.; Lu, Z.; Badgwell, D.; Mills, G.B.; et al. Prevention and early detection of ovarian cancer: Mission impossible? *Recent Results Cancer Res.* **2007**, *174*, 91–100.
3. Jemal, A.; Siegel, R.; Ward, E.; Murray, T.; Xu, J.; Thun, M.J. Cancer statistics, 2007. *CA Cancer J. Clin.* **2007**, *57*, 43–66.
4. Ferlay, J.; Shin, H.R.; Bray, F.; Forman, D.; Mathers, C.; Parkin, D.M. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int. J. Cancer* **2010**, *127*, 2893–2917.
5. Karst, A.M.; Drapkin, R. Ovarian cancer pathogenesis: A model in evolution. *J. Oncol.* **2010**, *2010*, 932371.
6. Lugani, Y.; Asthana, S.; Labani, S. Ovarian carcinoma: An overview of current status. *Adv. Mod. Oncol. Res.* **2016**, *2*, 261–270.
7. Robert, J.; Kurman, E. *Blaustein's Pathology of the Female Genital Tract*, 5th ed.; Springer: New York, NY, USA, 2002; Available online: **https://search.library.wisc.edu/catalog/999947979402121** (accessed on 2023).
8. Cathro, H. Pathology of the Ovary, first edition, 330 pp ($129.00): Author: Jaime Prat, M.D., F.R.C.Path. W.B. Saunders, Elsevier, Philadelphia, 2004. *Diagn. Cytopathol.* **2006**, *34*, 307.
9. Hanby, A.M.; Walker, C.; Tavassoli, F.A.; Devilee, P. Pathology and Genetics: Tumours of the Breast and Female Genital Organs. WHO Classification of Tumours series—Volume IV. Lyon, France: IARC Press. *Breast Cancer Res.* **2004**, *6*, 133.
10. Singh, A.; Gupta, S.; Sachan, M. Epigenetic Biomarkers in the Management of Ovarian Cancer: Current Prospectives. *Front. Cell Dev. Biol.* **2019**, *7*, 182.
11. Prahm, K.P.; Karlsen, M.A.; Høgdall, E.; Scheller, N.M.; Lundvall, L.; Nedergaard, L.; Christensen, I.J.; Høgdall, C. The prognostic value of dividing epithelial ovarian cancer into type I and type II tumors based on pathologic characteristics. *Gynecol. Oncol.* **2015**, *136*, 205–211.
12. Alcázar, J.L.; Utrilla-Layna, J.; Mínguez, J.; Jurado, M. Clinical and ultrasound features of type I and type II epithelial ovarian cancer. *Int. J. Gynecol. Cancer* **2013**, *23*, 680–684.
13. Kurman, R.J.; Shih, I.M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—Shifting the paradigm. *Hum. Pathol.* **2011**, *42*, 918–931.
14. Kurman, R.J.; Shih, I.M. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. *Am. J. Pathol.* **2016**, *186*, 733–747.
15. Stewart, B.W.; Kleihues, P. (Eds.) *World Cancer Report*; IARC Press: Lyon, France, 2003; Available online: **https://books.google.gr/books?id=CezHngEACAAJ** (accessed on 2023).

16. Ece, G.; Tuba, G. The Role of Circulating Biomarkers in the Early Diagnosis of Ovarian Cancer. In *Ovarian Cancer*; Omer, D., Andreas, P., Eds.; IntechOpen: Rijeka, Croatia, 2018; Chapter 7.

17. Grayson, K.; Gregory, E.; Khan, G.; Guinn, B.A. Urine Biomarkers for the Early Detection of Ovarian Cancer—Are We There Yet? *Biomark Cancer* **2019**, *11*.

18. Normanno, N.; Apostolidis, K.; de Lorenzo, F.; Beer, P.A.; Henderson, R.; Sullivan, R.; Biankin, A.V.; Horgan, D.; Lawler, M. Cancer Biomarkers in the era of precision oncology: Addressing the needs of patients and health systems. *Semin. Cancer Biol.* **2022**, *84*, 293–301.

19. Duffy, M.J. Tumor markers in clinical practice: A review focusing on common solid cancers. *Med. Princ. Pract.* **2013**, *22*, 4–11.

20. Chandra, K.B.; Yadav, S. Biomarkers in ovarian cancer and saliva: An update. *J. Reprod. Healthc. Med.* **2021**, *2*, 1.

21. Yang, J.; Xiang, C.; Liu, J. Clinical significance of combining salivary mRNAs and carcinoembryonic antigen for ovarian cancer detection. *Scand J. Clin. Lab. Investig.* **2021**, *81*, 39–45.

22. Furrer, D.; Grégoire, J.; Turcotte, S.; Plante, M.; Bachvarov, D.; Trudel, D.; Têtu, B.; Douville, P.; Bairati, I. Performance of preoperative plasma tumor markers HE4 and CA125 in predicting ovarian cancer mortality in women with epithelial ovarian cancer. *PLoS ONE* **2019**, *14*, e0218621.

23. Ueland, F.R. A Perspective on Ovarian Cancer Biomarkers: Past, Present and Yet-To-Come. *Diagnostics* **2017**, *7*, 14.

24. Charkhchi, P.; Cybulski, C.; Gronwald, J.; Wong, F.O.; Narod, S.A.; Akbari, M.R. CA125 and Ovarian Cancer: A Comprehensive Review. *Cancers* **2020**, *12*, 3730.

25. Cooper, B.C.; Sood, A.K.; Davis, C.S.; Ritchie, J.M.; Sorosky, J.I.; Anderson, B.; Buller, R.E. Preoperative CA 125 levels: An independent prognostic factor for epithelial ovarian cancer. *Obstet. Gynecol.* **2002**, *100*, 59–64.

26. Bottoni, P.; Scatena, R. The Role of CA 125 as Tumor Marker: Biochemical and Clinical Aspects. *Adv. Exp. Med. Biol.* **2015**, *867*, 229–244.

27. Rustin, G.J.; Vergote, I.; Eisenhauer, E.; Pujade-Lauraine, E.; Quinn, M.; Thigpen, T.; du Bois, A.; Kristensen, G.; Jakobsen, A.; Sagae, S.; et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int. J. Gynecol. Cancer* **2011**, *21*, 419–423.

28. Lee, M.; Chang, M.Y.; Yoo, H.; Lee, K.E.; Chay, D.B.; Cho, H.; Kim, S.; Kim, Y.T.; Kim, J.H. Clinical Significance of CA125 Level after the First Cycle of Chemotherapy on Survival of Patients with Advanced Ovarian Cancer. *Yonsei Med. J.* **2016**, *57*, 580–587.

29. Zhang, D.; Jiang, Y.X.; Luo, S.J.; Zhou, R.; Jiang, Q.X.; Hua, L. 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.

30. Rustin, G.J. Use of CA-125 to assess response to new agents in ovarian cancer trials. *J. Clin. Oncol.* **2003**, *21*, 187s–193s.

31. Tuxen, M.K.; Sölétormos, G.; Dombernowsky, P. Serum tumour marker CA 125 in monitoring of ovarian cancer during first-line chemotherapy. *Br. J. Cancer* **2001**, *84*, 1301–1307.

32. Lindemann, K.; Kristensen, G.; Mirza, M.R.; Davies, L.; Hilpert, F.; Romero, I.; Ayhan, A.; Burges, A.; Rubio, M.J.; Raspagliesi, F.; et al. Poor concordance between CA-125 and RECIST at the time of disease progression in patients with platinum-resistant ovarian cancer: Analysis of the AURELIA trial. *Ann. Oncol.* **2016**, *27*, 1505–1510

33. Liefers-Visser, J.A.L.; Meijering, R.A.M.; Reyners, A.K.L.; van der Zee, A.G.J.; de Jong, S. IGF system targeted therapy: Therapeutic opportunities for ovarian cancer. *Cancer Treat. Rev.* **2017**, *60*, 90–99.

34. Kang, S.; Seo, S.S.; Park, S.Y. Nadir CA-125 level is an independent prognostic factor in advanced epithelial ovarian cancer. *J. Surg. Oncol.* **2009**, *100*, 244–247.

35. Prat, A.; Parera, M.; Peralta, S.; Perez-Benavente, M.A.; Garcia, A.; Gil-Moreno, A.; Martinez-Palones, J.M.; Roxana, I.; Baselga, J.; Del Campo, J.M. Nadir CA-125 concentration in the normal range as an independent prognostic factor for optimally treated advanced epithelial ovarian cancer. *Ann. Oncol.* **2008**, *19*, 327–331.

36. Bast, R.C., Jr.; Klug, T.L.; St John, E.; Jenison, E.; Niloff, J.M.; Lazarus, H.; Berkowitz, R.S.; Leavitt, T.; Griffiths, C.T.; Parker, L.; et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N. Engl. J. Med.* **1983**, *309*, 883–887.

37. Akinwunmi, B.O.; Babic, A.; Vitonis, A.F.; Cramer, D.W.; Titus, L.; Tworoger, S.S.; Terry, K.L. Chronic Medical Conditions and CA125 Levels among Women without Ovarian Cancer. *Cancer Epidemiol. Biomark. Prev.* **2018**, *27*, 1483–1490.

38. Crosby, D.A.; Glover, L.E.; Martyn, F.; Wingfield, M. CA125 measured during menstruation can be misleading. *Ir. Med. J.* **2018**, *111*, 738.

39. Cramer, D.W.; O'Rourke, D.J.; Vitonis, A.F.; Matulonis, U.A.; Dijohnson, D.A.; Sluss, P.M.; Crum, C.P.; Liu, B.C. CA125 immune complexes in ovarian cancer patients with low CA125 concentrations. *Clin. Chem.* **2010**, *56*, 1889–1892.

40. Buys, S.S.; Partridge, E.; Black, A.; Johnson, C.C.; Lamerato, L.; Isaacs, C.; Reding, D.J.; Greenlee, R.T.; Yokochi, L.A.; Kessel, B.; et al. Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* **2011**, *305*, 2295–2303.

41. Henderson, J.T.; Webber, E.M.; Sawaya, G.F. Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* **2018**, *319*, 595–606.

42. Jacobs, I.J.; Menon, U.; Ryan, A.; Gentry-Maharaj, A.; Burnell, M.; Kalsi, J.K.; Amso, N.N.; Apostolidou, S.; Benjamin, E.; Cruickshank, D.; et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial. *Lancet* **2016**, *387*, 945–956.

43. Jacobs, I.J.; Skates, S.J.; MacDonald, N.; Menon, U.; Rosenthal, A.N.; Davies, A.P.; Woolas, R.; Jeyarajah, A.R.; Sibley, K.; Lowe, D.G.; et al. Screening for ovarian cancer: A pilot randomised controlled trial. *Lancet* **1999**, *353*, 1207–1210.

44. Hellstrom, I.; Heagerty, P.J.; Swisher, E.M.; Liu, P.; Jaffar, J.; Agnew, K.; Hellstrom, K.E. Detection of the HE4 protein in urine as a biomarker for ovarian neoplasms. *Cancer Lett.* **2010**, *296*, 43–48.

45. Kirwan, A.; Utratna, M.; O'Dwyer, M.E.; Joshi, L.; Kilcoyne, M. Glycosylation-Based Serum Biomarkers for Cancer Diagnostics and Prognostics. *Biomed. Res. Int.* **2015**, *2015*, 490531.

46. Nalini, N.; Kumar, A.; Sharma, S.; Singh, B.; Singh, A.V.; Prakash, J.; Singh, S. The Diagnostic Accuracy of Serum and Urine Human Epididymis Protein 4 (HE4) in Ovarian Cancer in 15,394 Subjects: An Updated Meta-Analysis. *Cureus* **2022**, *14*, e30457.

47. Barr, C.E.; Funston, G.; Jeevan, D.; Sundar, S.; Mounce, L.T.A.; Crosbie, E.J. The Performance of HE4 Alone and in Combination with CA125 for the Detection of Ovarian Cancer in an Enriched Primary Care Population. *Cancers* **2022**, *14*, 2124.

48. Chudecka-Głaz, A.; Cymbaluk-Płoska, A.; Wężowska, M.; Menkiszak, J. Could HE4 level measurements during first-line chemotherapy predict response to treatment among ovarian cancer patients? *PLoS ONE* **2018**, *13*, e0194270.

49. Arora, R.P.; Abhilash, V.; Vemanamandi, P. Diagnostic accuracy of HE4 and risk of ovarian malignancy algorithm in prediction of ovarian cancer in patients with pelvic mass: A regional cancer centre experience. *Int. J. Reprod. Contracept. Obstet. Gynecol.* **2022**, *11*, 1531–1538.

50. Ong, C.; Biswas, A.; Choolani, M.A.; Low, J.J.H. Comparison of risk of malignancy indices in evaluating ovarian masses in a Southeast Asian population. *Singap. Med. J.* **2013**, *54*, 136–139.

51. Chudecka-Głaz, A.; Strojna, A.; Michalczyk, K.; Wieder-Huszla, S.; Safranow, K.; Skwirczyńska, E.; Jurczak, A. Evaluation of He4 Use in the Diagnosis of Ovarian Cancer: First and Second Recurrence, and an Analysis of HE4 Concentration during Second- and Third-Line Chemotherapy. *Diagnostics* **2023**, *13*, 452.

52. Moore, R.G.; Hill, E.K.; Horan, T.; Yano, N.; Kim, K.; MacLaughlan, S.; Lambert-Messerlian, G.; Tseng, Y.D.; Padbury, J.F.; Miller, M.C.; et al. HE4 (WFDC2) gene overexpression promotes ovarian tumor growth. *Sci. Rep.* **2014**, *4*, 3574.

53. Hellström, I.; Raycraft, J.; Hayden-Ledbetter, M.; Ledbetter, J.A.; Schummer, M.; McIntosh, M.; Drescher, C.; Urban, N.; Hellström, K.E. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. *Cancer Res.* **2003**, *63*, 3695–3700.

54. Moore, R.G.; McMeekin, D.S.; Brown, A.K.; DiSilvestro, P.; Miller, M.C.; Allard, W.J.; Gajewski, W.; Kurman, R.; Bast, R.C., Jr.; Skates, S.J. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecol. Oncol.* **2009**, *112*, 40–46.

55. Heitz, F.; Lakis, S.; Harter, P.; Heikaus, S.; Sehouli, J.; Talwar, J.; Menon, R.; Ataseven, B.; Bertrand, M.; Schneider, S.; et al. Cell-free tumor DNA, CA125 and HE4 for the objective assessment of tumor burden in patients with advanced high-grade serous ovarian cancer. *PLoS ONE* **2022**, *17*, e0262770.

56. Moore, R.G.; Jabre-Raughley, M.; Brown, A.K.; Robison, K.M.; Miller, M.C.; Allard, W.J.; Kurman, R.J.; Bast, R.C.; Skates, S.J. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. *Am. J. Obstet. Gynecol.* **2010**, *203*, 228.e1–228.e6.

57. Van Gorp, T.; Cadron, I.; Despierre, E.; Daemen, A.; Leunen, K.; Amant, F.; Timmerman, D.; De Moor, B.; Vergote, I. HE4 and CA125 as a diagnostic test in ovarian cancer: Prospective validation of the Risk of Ovarian Malignancy Algorithm. *Br. J. Cancer* **2011**, *104*, 863–870.

58. Samborski, A.; Miller, M.C.; Blackman, A.; MacLaughlan-David, S.; Jackson, A.; Lambert-Messerlian, G.; Rowswell-Turner, R.; Moore, R.G. HE4 and CA125 serum biomarker monitoring in women with epithelial ovarian cancer. *Tumour Biol.* **2022**, *44*, 205–213.

59. Huhtinen, K.; Suvitie, P.; Hiissa, J.; Junnila, J.; Huvila, J.; Kujari, H.; Setälä, M.; Härkki, P.; Jalkanen, J.; Fraser, J.; et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. *Br. J. Cancer* **2009**, *100*, 1315–1319.

60. Moore, R.G.; Brown, A.K.; Miller, M.C.; Skates, S.; Allard, W.J.; Verch, T.; Steinhoff, M.; Messerlian, G.; DiSilvestro, P.; Granai, C.O.; et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecol. Oncol.* **2008**, *108*, 402–408.

61. Leandersson, P.; Åkesson, A.; Hedenfalk, I.; Malander, S.; Borgfeldt, C. A multiplex biomarker assay improves the diagnostic performance of HE4 and CA125 in ovarian tumor patients. *PLoS ONE* **2020**, *15*, e0240418.

62. Scambia, G.; Benedetti Panici, P.; Baiocchi, G.; Perrone, L.; Greggi, S.; Mancuso, S. CA 15-3 as a tumor marker in gynecological malignancies. *Gynecol. Oncol.* **1988**, *30*, 265–273.

63. Bian, J.; Li, B.; Kou, X.J.; Liu, T.Z.; Ming, L. Clinical significance of combined detection of serum tumor markers in diagnosis of patients with ovarian cancer. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 6241–6243.

64. Zhang, Z.; Yu, Y.; Xu, F.; Berchuck, A.; van Haaften-Day, C.; Havrilesky, L.J.; de Bruijn, H.W.; van der Zee, A.G.; Woolas, R.P.; Jacobs, I.J.; et al. Combining multiple serum tumor markers improves detection of stage I epithelial ovarian cancer. *Gynecol. Oncol.* **2007**, *107*, 526–531.

65. Ali, F.T.; Soliman, R.M.; Hassan, N.S.; Ibrahim, A.M.; El-Gizawy, M.M.; Mandoh, A.A.Y.; Ibrahim, E.A. Sensitivity and specificity of microRNA-204, CA125, and CA19.9 as biomarkers for diagnosis of ovarian cancer. *PLoS ONE* **2022**, *17*, e0272308.

66. Lertkhachonsuk, A.A.; Buranawongtrakoon, S.; Lekskul, N.; Rermluk, N.; Wee-Stekly, W.W.; Charakorn, C. Serum CA19-9, CA-125 and CEA as tumor markers for mucinous ovarian tumors. *J. Obstet. Gynaecol. Res.* **2020**, *46*, 2287–2291.

67. Whittington, J.; Fantz, C.R.; Gronowski, A.M.; McCudden, C.; Mullins, R.; Sokoll, L.; Wiley, C.; Wilson, A.; Grenache, D.G. The analytical specificity of human chorionic gonadotropin assays determined using WHO International Reference Reagents. *Clin. Chim. Acta* **2010**, *411*, 81–85.

68. Zhong, Y.; Wang, Y.; Huang, J.; Xu, X.; Pan, W.; Gao, S.; Zhang, Y.; Su, M. Association of hCG and LHCGR expression patterns with clinicopathological parameters in ovarian cancer. *Pathol. Res. Pract.* **2019**, *215*, 748–754.

69. Lenhard, M.; Tsvilina, A.; Schumacher, L.; Kupka, M.; Ditsch, N.; Mayr, D.; Friese, K.; Jeschke, U. Human chorionic gonadotropin and its relation to grade, stage and patient survival in ovarian cancer. *BMC Cancer* **2012**, *12*, 2.

70. Mandai, M.; Konishi, I.; Kuroda, H.; Fujii, S. LH/hCG action and development of ovarian cancer—A short review on biological and clinical/epidemiological aspects. *Mol. Cell Endocrinol.* **2007**, *269*, 61–64.

71. Vartiainen, J.; Lehtovirta, P.; Finne, P.; Stenman, U.H.; Alfthan, H. Preoperative serum concentration of hCGbeta as a prognostic factor in ovarian cancer. *Int. J. Cancer* **2001**, *95*, 313–316.

72. Djurdjevic, S.; Maksimovic, M.; Pantelic, M.; Golubovic, A.; Curcic, A. Usefulness of beta hCG as tumor marker in the diagnosis and follow up of patients with ovarian cancer. *J. BUON* **2011**, *16*, 715–721.

73. Wu, W.; Gao, H.; Li, X.; Peng, S.; Yu, J.; Liu, N.; Zhan, G.; Zhu, Y.; Wang, K.; Guo, X. β-hCG promotes epithelial ovarian cancer metastasis through ERK/MMP2 signaling pathway. *Cell Cycle* **2019**, *18*, 46–59.

74. Robertson, D.M.; Pruysers, E.; Jobling, T. Inhibin as a diagnostic marker for ovarian cancer. *Cancer Lett.* **2007**, *249*, 14–17.

75. Robertson, D.M.; Cahir, N.; Burger, H.G.; Mamers, P.; McCloud, P.I.; Pettersson, K.; McGuckin, M. Combined inhibin and CA125 assays in the detection of ovarian cancer. *Clin. Chem.* **1999**, *45*, 651–658.

76. McNeilly, A.S. Diagnostic applications for inhibin and activins. *Mol. Cell Endocrinol.* **2012**, *359*, 121–125.

77. Robertson, D.M.; Pruysers, E.; Burger, H.G.; Jobling, T.; McNeilage, J.; Healy, D. Inhibins and ovarian cancer. *Mol. Cell Endocrinol.* **2004**, *225*, 65–71.

78. Robertson, D.M.; Stephenson, T.; Pruysers, E.; Burger, H.G.; McCloud, P.; Tsigos, A.; Groome, N.; Mamers, P.; McNeilage, J.; Jobling, T.; et al. Inhibins/activins as diagnostic markers for ovarian cancer. *Mol. Cell Endocrinol.* **2002**, *191*, 97–103.

79. Singh, S.A.; Dahshan, B.; Krc, R.F.; McDermott, D.M.; Jacobson, G.M. Radiographic and Tumor Biomarker Response to Radiotherapy for Recurrent Granulosa Cell Tumor of the Ovary. *Cureus* **2021**, *13*, e13154.

80. Burger, H.G.; Fuller, P.J.; Chu, S.; Mamers, P.; Drummond, A.; Susil, B.; Neva, P.; Robertson, D.M. The inhibins and ovarian cancer. *Mol. Cell Endocrinol.* **2001**, *180*, 145–148.

81. Chen, J.; Wang, J.; Cao, D.; Yang, J.; Shen, K.; Huang, H.; Shi, X. Alpha-fetoprotein (AFP)-producing epithelial ovarian carcinoma (EOC): A retrospective study of 27 cases. *Arch. Gynecol. Obstet.* **2021**, *304*, 1043–1053.

82. Bian, J.; Li, B.; Kou, X.J.; Wang, X.N.; Sun, X.X.; Ming, L. Clinical applicability of multi-tumor marker protein chips for diagnosing ovarian cancer. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 8409–8411.

83. Isonishi, S.; Ogura, A.; Kiyokawa, T.; Suzuki, M.; Kunito, S.; Hirama, M.; Tachibana, T.; Ochiai, K.; Tanaka, T. Alpha-fetoprotein (AFP)-producing ovarian tumor in an elderly woman. *Int. J. Clin. Oncol.* **2009**, *14*, 70–73.

84. Aggarwal, P.; Kehoe, S. Serum tumour markers in gynaecological cancers. *Maturitas* **2010**, *67*, 46–53.

85. Zhang, F.; Zhang, Z.L. The Diagnostic Value of Transvaginal Sonograph (TVS), Color Doppler, and Serum Tumor Marker CA125, CEA, and AFP in Ovarian Cancer. *Cell Biochem. Biophys.* **2015**, *72*, 353–357.

86. Boran, N.; Kayikçioğlu, F.; Yalvaç, S.; Tulunay, G.; Ekinci, U.; Köse, M.F. Significance of serum and peritoneal fluid lactate dehydrogenase levels in ovarian cancer. *Gynecol. Obstet. Investig.* **2000**, *49*, 272–274.

87. Bastani, A.; Asghary, A.; Heidari, M.H.; Karimi-Busheri, F. Evaluation of the sensitivity and specificity of serum level of prostasin, CA125, LDH, AFP, and hCG+β in epithelial ovarian cancer patients. *Eur. J. Gynaecol. Oncol.* **2017**, *38*, 418–424.

88. Macfarlane, L.A.; Murphy, P.R. MicroRNA: Biogenesis, Function and Role in Cancer. *Curr. Genom.* **2010**, *11*, 537–561.

89. Aboutalebi, H.; Bahrami, A.; Soleimani, A.; Saeedi, N.; Rahmani, F.; Khazaei, M.; Fiuji, H.; Shafiee, M.; Ferns, G.A.; Avan, A.; et al. The diagnostic, prognostic and therapeutic potential of circulating microRNAs in ovarian cancer. *Int. J. Biochem. Cell Biol.* **2020**, *124*, 105765.

90. Bartel, D.P. MicroRNAs: Target recognition and regulatory functions. *Cell* **2009**, *136*, 215–233.

91. Pritchard, C.C.; Cheng, H.H.; Tewari, M. MicroRNA profiling: Approaches and considerations. *Nat. Rev. Genet.* **2012**, *13*, 358–369.

92. Nakamura, K.; Sawada, K.; Yoshimura, A.; Kinose, Y.; Nakatsuka, E.; Kimura, T. Clinical relevance of circulating cell-free microRNAs in ovarian cancer. *Mol. Cancer* **2016**, *15*, 48.

93. Mitchell, P.S.; Parkin, R.K.; Kroh, E.M.; Fritz, B.R.; Wyman, S.K.; Pogosova-Agadjanyan, E.L.; Peterson, A.; Noteboom, J.; O'Briant, K.C.; Allen, A.; et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 10513–10518.

94. Prahm, K.P.; Novotny, G.W.; Høgdall, C.; Høgdall, E. Current status on microRNAs as biomarkers for ovarian cancer. *Apmis* **2016**, *124*, 337–355.

95. Llauradó, M.; Majem, B.; Altadill, T.; Lanau, L.; Castellví, J.; Sánchez-Iglesias, J.L.; Cabrera, S.; De la Torre, J.; Díaz-Feijoo, B.; Pérez-Benavente, A.; et al. MicroRNAs as prognostic markers in ovarian cancer. *Mol. Cell Endocrinol.* **2014**, *390*, 73–84.

96. Katz, B.; Tropé, C.G.; Reich, R.; Davidson, B. MicroRNAs in Ovarian Cancer. *Hum. Pathol.* **2015**, *46*, 1245–1256.

97. Yokoi, A.; Yoshioka, Y.; Hirakawa, A.; Yamamoto, Y.; Ishikawa, M.; Ikeda, S.I.; Kato, T.; Niimi, K.; Kajiyama, H.; Kikkawa, F.; et al. A combination of circulating miRNAs for the early detection of ovarian cancer. *Oncotarget* **2017**, *8*, 89811–89823.

98. Widschwendter, M.; Zikan, M.; Wahl, B.; Lempiäinen, H.; Paprotka, T.; Evans, I.; Jones, A.; Ghazali, S.; Reisel, D.; Eichner, J.; et al. The potential of circulating tumor DNA methylation analysis for the early detection and management of ovarian cancer. *Genome Med.* **2017**, *9*, 116.

99. Chen, X.; Gole, J.; Gore, A.; He, Q.; Lu, M.; Min, J.; Yuan, Z.; Yang, X.; Jiang, Y.; Zhang, T.; et al. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. *Nat. Commun.* **2020**, *11*, 3475.

100. Fiala, C.; Diamandis, E.P. Can a Broad Molecular Screen Based on Circulating Tumor DNA Aid in Early Cancer Detection? *J. Appl. Lab. Med.* **2020**, *5*, 1372–1377.

101. Ortiz-Muñoz, B.; Aznar-Oroval, E.; García García, A.; Covisa Peris, A.; Perez Ballestero, P.; Sanchez Yepes, M.; Garcia Lozano, T.; Illueca Ballester, C.; García Garcia, E. HE4, Ca125 and ROMA algorithm for differential diagnosis between benign gynaecological diseases and ovarian cancer. *Tumour Biol.* **2014**, *35*, 7249–7258.

102. Dong, R.; Yu, J.; Pu, H.; Zhang, Z.; Xu, X. Frequent SLIT2 promoter methylation in the serum of patients with ovarian cancer. *J. Int. Med. Res.* **2012**, *40*, 681–686.

103. Esteller, M.; Silva, J.M.; Dominguez, G.; Bonilla, F.; Matias-Guiu, X.; Lerma, E.; Bussaglia, E.; Prat, J.; Harkes, I.C.; Repasky, E.A.; et al. Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. *J. Natl. Cancer Inst.* **2000**, *92*, 564–569.

104. Zhang, Q.; Hu, G.; Yang, Q.; Dong, R.; Xie, X.; Ma, D.; Shen, K.; Kong, B. A multiplex methylation-specific PCR assay for the detection of early-stage ovarian cancer using cell-free serum DNA. *Gynecol. Oncol.* **2013**, *130*, 132–139.

105. Integrated genomic analyses of ovarian carcinoma. *Nature* **2011**, *474*, 609–615.

106. Lu, H.; Liu, Y.; Wang, J.; Fu, S.; Wang, L.; Huang, C.; Li, J.; Xie, L.; Wang, D.; Li, D.; et al. Detection of ovarian cancer using plasma cell-free DNA methylomes. *Clin. Epigenetics* **2022**, *14*, 74.

107. Ebata, T.; Yamashita, S.; Takeshima, H.; Yoshida, H.; Kawata, Y.; Kino, N.; Yasugi, T.; Terao, Y.; Yonemori, K.; Kato, T.; et al. DNA methylation marker to estimate ovarian cancer cell fraction. *Med. Oncol.* **2022**, *39*, 78.

108. Cunningham, J.M.; Winham, S.J.; Wang, C.; Weiglt, B.; Fu, Z.; Armasu, S.M.; McCauley, B.M.; Brand, A.H.; Chiew, Y.E.; Elishaev, E.; et al. DNA Methylation Profiles of Ovarian Clear Cell Carcinoma. *Cancer Epidemiol. Biomark. Prev.* **2022**, *31*, 132–141.

109. Yin, L.; Zhang, N.; Yang, Q. DNA methylation subtypes for ovarian cancer prognosis. *FEBS Open Bio* **2021**, *11*, 851–865.

110. Yang, Y.; Wu, L.; Shu, X.; Lu, Y.; Shu, X.O.; Cai, Q.; Beeghly-Fadiel, A.; Li, B.; Ye, F.; Berchuck, A.; et al. Genetic Data from Nearly 63,000 Women of European Descent Predicts DNA Methylation Biomarkers and Epithelial Ovarian Cancer Risk. *Cancer Res.* **2019**, *79*, 505–517.

الملخص:

الخلفية: لا يزال سرطان المبيض (OC) واحدًا من أخطر أنواع السرطان النسائي، مع عدد كبير من الحالات التي يتم تشخيصها في مراحل متقدمة، مما يؤدي إلى نتائج بقاء ضعيفة. يعد الكشف المبكر تحديًا رئيسيًا، حيث أن الطرق التقليدية، بما في ذلك العلاج الكيميائي التقليدي، غالبًا ما تكون غير فعّالة في التشخيصات المتأخرة. نظرًا

لأن أقل من 20% من الحالات يتم اكتشافها في مرحلة مبكرة، فإن البحث عن علامات حيوية تشخيصية موثوقة أمر بالغ الأهمية. تقدم هذه المراجعة تحليلًا محدثًا للعلامات الحيوية المتعلقة بتشخيص سرطان المبيض، مع التركيز على أهميتها وفائدتها السريرية.

الهدف: يهدف هذا المراجعة إلى تحديث الفهم الحالي للعلامات الحيوية لسرطان المبيض، مع التركيز بشكل خاص على CA-125 وHE4 ، ودورهما التشخيصي، وإمكاناتهما في تحسين الكشف المبكر، والتنبؤ بالمرض، ومراقبة استجابة العلاج.

الطرق: تقوم هذه المراجعة بتلخيص نتائج الدراسات الحديثة حول علامات سرطان المبيض الحيوية، وخاصة CA-125 و .HE4 تم إجراء تحليل مفصل لفعاليتهما التشخيصية، والحساسية، والخصوصية، والقيود. تم تضمين تحليل ميتا لدراسات تتعلق بـ HE4 و CA-125 لتقييم إمكانياتهما في اكتشاف سرطان المبيض.

النتائج: يعتبر CA-125 هو أكثر العلامات الحيوية المستخدمة على نطاق واسع، إلا أن له قيودًا في الخصوصية، وغالبًا ما يؤدي إلى نتائج إيجابية كاذبة في الحالات الحميدة. على الرغم من فائدته السريرية في تتبع تقدم المرض، فإن دوره في الكشف المبكر محدود. من ناحية أخرى، أظهر HE4 حساسية وخصوصية أعلى، خاصة في التمييز بين أنواع مختلفة من أورام المبيض. يزيد استخدام CA-125 و HE4 معًا في الخوارزميات مثل ROMA من دقة التشخيص. تظهر الدراسات أن هذه العلامات الحيوية، خاصة في المراحل المتقدمة، تقدم معلومات تنبؤية قيمة.

الخلاصة: يُظهر كل من CA-125 و HE4 وعدًا في تعزيز تشخيص سرطان المبيض، حيث يقدم HE4 نهجًا أكثر تحديدًا وحساسية. عند استخدامهما معًا، تعزز هذه العلامات الحيوية بشكل كبير احتمال الكشف المبكر، مما يوفر أملًا في نتائج أفضل. تعتبر الأبحاث المستقبلية حول العلامات الحيوية الأخرى وطرق الكشف المحسنة أمرًا أساسيًا لتطوير تشخيص سرطان المبيض وزيادة معدلات بقاء المرضى.

الكلمات المفتاحية: سرطان المبيض، العلامات الحيوية، CA-125، HE4، الكشف المبكر، التشخيص، التنبؤ بالمرض، سرطان المبيض الظهاري(EOC) ، فحص السرطان.