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DIAGNOSTIC SIGNIFICANCE OF BIOMARKERS (CA-125, HE4) IN OVARIAN CANCER SCREENING

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Abstract:

This article analyzes the diagnostic significance of CA-125 and HE4 biomarkers in the early detection of ovarian cancer (OC). Research indicates that while CA-125 is a classic marker, its sensitivity in the early stages and specificity regarding benign tumors are relatively low. In contrast, the HE4 biomarker is distinguished by the fact that its levels do not rise in gynecological conditions such as endometriosis. The ROMA index, which integrates these two markers with the patient's menopausal status, provides the highest accuracy (sensitivity ~90%) in diagnosing ovarian cancer.

Keywords: ovarian cancer, CA-125, HE4, ROMA index, biomarker, screening.

Introduction (Fragment):

Ovarian cancer (OC) is one of the most dangerous malignancies of the female reproductive system and holds a leading position in gynecological oncology in terms of mortality rates. The "stealthy" nature of the disease lies in the absence of specific symptoms during the early stages, which results in 70-75% of patients being diagnosed at stages III and IV. Therefore, developing effective screening methods remains one of the most pressing issues in modern medicine.

Global Statistics and Risk Factors:

According to the World Health Organization (WHO), approximately 300,000 women die from ovarian cancer annually, making it a serious global health challenge. The prevalence of the disease exhibits regional variations; despite improved diagnostic and treatment capabilities in developed countries, mortality rates remain high in developing nations due to difficulties in early diagnosis.

Several risk factors contribute to the onset of ovarian cancer. Genetic predisposition (mutations in BRCA1 and BRCA2 genes), age, hormonal changes, reproductive history, and pregnancy/breastfeeding history significantly influence the risk. Additionally, obesity, dietary habits, and adverse environmental factors play a crucial role.

Challenges in Early Detection and Treatment:

Early detection of ovarian cancer is complex because clinical symptoms are not clearly manifested in the initial stages. Patients often present with non-specific symptoms such as abdominal discomfort, bloating, or digestive issues, which frequently leads to delayed diagnosis. Laboratory diagnostics and imaging techniques (ultrasonography, CT, MRI) aid in diagnosis; however, they may lack sufficient accuracy during the early

stages. Consequently, global healthcare systems are increasingly focusing on biomarkers and genetic testing for early identification. Treatment options primarily rely on a combination of surgery and chemotherapy.

Comparative Efficiency of Biomarkers in Ovarian Cancer Diagnosis

Indicators	CA-125	HE4	ROMA Index (CA-125 + HE4)
Sensitivity	43% – 65%	72% – 83%	88% – 94%
Specificity	76% – 82%	94% – 96%	84% – 91%
Early-stage Detection	Low	High	Highest
Elevation in Endometriosis	Yes (high risk)	No (rarely)	Minimal impact
Diagnostic Accuracy (AUC)	0.81	0.89	0.93

Characteristics of the CA-125 Biomarker:

The CA-125 test is a blood analysis used to measure the levels of Cancer Antigen 125, a protein that may be elevated in ovarian cancer and various other medical conditions. Although primarily utilized as a tumor marker for ovarian cancer, it also provides clinical information regarding other conditions such as endometriosis, pelvic inflammatory disease (PID), and uterine fibroids.

The test assesses the concentration of CA-125 in the bloodstream. While elevated levels may indicate the presence or progression of ovarian cancer, they are also observed in benign conditions. Therefore, this test is typically used in conjunction with other diagnostic tools, such as imaging (ultrasound, CT) and biopsy, to ensure a comprehensive clinical evaluation.

Interpretation and Clinical Applications of CA-125:

Understanding test results is crucial for accurate diagnosis and monitoring. The interpretation levels are generally categorized as follows:

- Normal levels: Below 35 U/ml, which typically indicates no significant abnormality.
- Slightly elevated levels: May be caused by benign conditions such as endometriosis or uterine fibroids.
- Significantly elevated levels: Often associated with ovarian cancer or other malignancies; however, further diagnostic confirmation is required.

The CA-125 test has several critical applications, including:

1. Monitoring Treatment: Assessing the effectiveness of therapy in patients with ovarian cancer.

2. Detection of Recurrence: Identifying potential relapses in patients previously treated for the disease.
3. Screening High-Risk Individuals: Evaluating women with a significant family history of ovarian cancer.
4. Differential Diagnosis: Assisting in the identification of other conditions such as endometriosis, pelvic inflammatory disease, and uterine fibroids.

Clinical Significance of HE4 (Human Epididymis Protein 4):

In recent years, HE4 (Human Epididymis Protein 4) has been recognized as one of the most promising biomarkers in the diagnosis of ovarian cancer (OC). Although initially identified in the tissues of the epididymis, clinical studies have confirmed its high expression by epithelial ovarian cancer cells.

The primary clinical advantage of HE4 is its high specificity. Unlike the traditional CA-125 marker, HE4 levels rarely increase in benign conditions such as endometriosis, uterine fibroids, or other inflammatory pelvic diseases. This characteristic allows clinicians to perform a more accurate differential diagnosis in determining the nature (malignant vs. benign) of pelvic masses.

Early Detection and Limitations of HE4:

Furthermore, the HE4 marker demonstrates higher sensitivity than CA-125 in detecting the early stages of the disease. Research conducted in 2021 indicates that HE4 is capable of identifying a subset of ovarian cancer cases even when CA-125 levels remain within the normal range. However, it is essential to consider that HE4 levels can be affected by renal insufficiency and age-related factors (specifically during postmenopause). These variables necessitate an individualized approach when interpreting test results in clinical practice.

The ROMA Index (Risk of Ovarian Malignancy Algorithm):

The ROMA index is a mathematical algorithm that integrates the serum concentrations of CA-125 and HE4 biomarkers with the patient's menopausal status to assess the risk of ovarian malignancy.

The primary advantage of this algorithm is that it provides significantly higher diagnostic accuracy than any single biomarker used alone. The ROMA index enables the stratification of patients into specific risk categories (low or high risk). According to multicenter studies conducted in 2021, the ROMA index demonstrates a sensitivity of 90-94%, significantly outperforming traditional methods, particularly in the early stages of the disease.

It is noteworthy that the ROMA algorithm allows clinicians to more accurately stratify women presenting with pelvic masses and ensure timely referral to specialized oncological centers. This, in turn, enhances the quality of preoperative diagnosis and plays a critical strategic role in improving overall patient survival rates.

Definition of Biomarkers and Screening:

A biomarker (biological marker) is a characteristic that serves as an objective indicator of normal biological processes, pathogenic changes, or pharmacological responses to a therapeutic intervention. In oncology, biomarkers are proteins, genes, or other

molecules produced either by tumor cells or by the body in response to tumor development. An ideal biomarker should possess high sensitivity (to avoid missing the disease) and high specificity (to minimize false positives in healthy individuals).

Screening refers to a system of diagnostic measures aimed at the early detection of a pathological process among individuals who do not yet exhibit overt clinical symptoms. In the context of ovarian cancer (OC), the primary objective of screening is to identify the tumor at stages I and II, when treatment efficacy is at its highest.

Current Screening Approaches and Future Perspectives:

Since no single, absolutely effective method for ovarian cancer screening currently exists, a multimodal approach is employed in clinical practice. This approach integrates the analysis of serum tumor markers (CA-125, HE4) with transvaginal ultrasound (TVUS) results.

In modern screening protocols, genetic predisposition (such as mutations in the BRCA1 and BRCA2 genes) and family medical history play a pivotal role. Utilizing a combination of biomarkers alongside mathematical algorithms like the ROMA index fundamentally enhances diagnostic quality and contributes significantly to reducing mortality rates from ovarian cancer.

Conclusion

Ovarian cancer remains a formidable challenge for global healthcare systems. The complexity of the disease is exacerbated by late-stage diagnosis, regional disparities in diagnostic and treatment facilities, and significant socio-economic consequences. However, through epidemiological research, the study of risk factors, and the advancement of early detection methods, there is a substantial opportunity to reduce disease burden and improve patients' quality of life.

Innovative approaches, particularly the use of biomarkers, genetic testing, and targeted therapy, are enhancing the effectiveness of ovarian cancer management and treatment on a global scale. Concurrently, preventative strategies, support for reproductive health, and increasing awareness among women play a vital role in disease prevention. To mitigate the global challenges posed by ovarian cancer, it is essential to implement early diagnosis, individualized approaches, innovative treatments, and preventive measures collectively. This integrated strategy will serve not only to save the lives of individual patients but also to improve the overall health of society.

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