

HE4, CA 125 and ROMA: High performance tumor markers improving the diagnostics of ovarian cancer

Medical background

Ovarian cancer is one of the most frequent cancers in women with high mortality worldwide. The prognosis is still disappointing, since most ovarian cancer cases are detected in the late stages when the prospects of a successful cure and thus the survival rates are rather low. This is because in the early stages of ovarian cancer symptoms are unspecific and may even be completely absent. In later stages the malignancy can cause a pelvic mass with discomfort and pain. Consequently, new biochemical markers and concepts which can support in diagnosing ovarian cancer in the early stages are highly desirable.

For the early diagnosis of ovarian cancer, the mainstream diagnostic approach is based on the combination of CA 125 and ultrasonography. This procedure has disadvantages concerning the diagnostic accuracy of CA 125. Not only that the sensitivity is related to the tumor stage showing low sensitivity in the early stages I and II, the even greater problem is the obvious lack of specificity. Abnormal CA 125 serum levels can be found in many benign diseases and gynecological conditions like renal failure, liver cirrhosis, ovarian cysts and endometriosis as well as in several malignancies other than ovarian cancer, including endometrial and lung cancer and even lymphomas.

The novel tumor marker HE4 (human epididymal protein 4), part of a family of protease inhibitors that functions in protective immunity, is highly overexpressed in ovarian cancer. Compared to CA 125, HE4 exhibits a similar sensitivity but significantly higher specificity, excluding patients with renal failure where high levels were found. Numerous studies clearly show that the use of HE4 may be highly beneficial in the differential diagnosis of ovarian cancer with other gynecological conditions especially in premenopausal women. Although CA 125 is still found in the majority of oncology guidelines as tumor marker of the initial step, the diagnostic value of HE4 alone obviously exceeds that of the solitary determination of CA 125 in the diagnosis of ovarian cancer. The limited diagnostic performance of CA 125 alone - showing good discrimination between benign and malign processes foremost in the late stages - hereby highly benefits from the supplementary use of HE4 which allows such a discrimination also in the early stages.

	Sensitivity	Specificity	PPV	NPV
HE4	79 %	98%	97 %	93 %
CA 125	83 %	71 %	53 %	91 %
ROMA	90 %	88 %	74 %	96 %

PPV: positive predictive value, NPV: negative predictive value

For further improvement regarding sensitivity and specificity, we suggest the use of the Risk of Ovarian Malignancy Algorithm (ROMA-Score), including both CA 125 and HE4 and considering the menopausal status to stratify the ovarian cancer risk in patients with uncertain pelvic masses. Since it is the parameter with the highest

discrimination between ovarian cancer and benign gynecological diseases (see table), the ROMA-Score can be used to classify women into high and low risk groups allowing for an effective triage of women with respect to the subsequent appropriate surgical procedure and care.

The use of HE4 is not only beneficial in the first diagnosis, but also during the follow up. While in the majority of cancer patients both CA 125 and HE4 are expressed, there are also patients who are positive for only one of the biomarkers. For example, up to 20% of ovarian cancers lack expression of the CA 125 antigen. Thus the combination of CA125 and HE4 helps reducing the number of biomarker negative patients and delivering more confidence in monitoring the disease status.

In 2011, HE4 was finally approved by the US Food and Drug Administration (FDA) along with CA 125 for the use in Risk of Ovarian Malignancy Algorithm (ROMA).

Method and turnaround time

Electro-chemiluminescence immunoassay (ECLIA);
daily analysis, results same or next working day

Material

Serum, about 2 ml

Reference intervals & cut-offs

CA 125 < 35 U/ml

HE4 < 40 years: 60,5 pmol/l (95- percentile)
40-49 years: 76,2 pmol/l
50-59 years: 74,3 pmol/l
60-69 years: 82,9 pmol/l
≥ 70 years: 104 pmol/l

ROMA < 11,4 (premenopausal)
< 29,9 (postmenopausal)

Contact

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Literature

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2. Moore et al. Evaluation of the Diagnostic Accuracy of the Risk of Ovarian Malignancy Algorithm in Women with a Pelvic Mass. *Obstet Gynecol.* 2011 Aug;118 (2 Pt 1):280-8.
3. Assessing ovarian cancer risk with the ROMA algorithm - Combining CA 125 and HE4 tumor markers in pelvic mass evaluation. Roche Diagnostics International Ltd., Switzerland.
4. HE4 - Human Epididymal Protein 4: A novel oncological biomarker improving ovarian cancer care. Roche Diagnostics International Ltd., Switzerland.