HE4 – Human Epididymal Protein 4
A novel oncological biomarker improving ovarian cancer care
Ovarian cancer

Worldwide, ovarian cancer is the second leading cancer in women and the fourth common cause of dying from cancer. It is a gynecological disease with one of the highest mortality rates. The highest incidence is found in industrialized nations like North America, Europe, Australia and New Zealand. Worldwide more than 200,000 women are diagnosed with this disease and 140,000 die from it.\textsuperscript{1} Although therapeutic options like new pharmaceuticals and surgery have improved over the last years, the prognosis is still disappointing. The more the disease has progressed, the lower the survival rate is and unfortunately most of the ovarian cancer cases are detected in later stages where the chances for a cure are rather low.

In the early stages of ovarian cancer symptoms are unspecific and cause little, if any, discomfort. Later, women may suffer from so-called pelvic or adnexal masses which can result in abdominal pain. It is estimated that 5 to 10 percent of women will present with a pelvic mass to their physician during their lifetime and undergo a surgical procedure for a suspected ovarian malignancy. In approx. 13 to 21 percent of these women, ovarian malignancies will be found.\textsuperscript{2}

Therefore, new methods and biomarkers which can help in diagnosing this disease at an earlier stage are highly desirable.

The new biomarker HE4 (human epididymal protein 4) together with the already established marker CA125 can play a very important role here.

Human epididymal protein 4 (HE4) was first detected in the epithelia of the distal epididymis.\textsuperscript{3} In epithelial ovarian cancer (EOC) tissue and in serum of patients with EOC, very high concentrations of HE4 can be found.\textsuperscript{4} Therefore, the risk assessment of epithelial ovarian cancer (EOC) is expected to be supported by measuring HE4.

Furthermore, HE4 was also shown to be an independent prognostic marker for ovarian cancer.\textsuperscript{5}

![Fig. 1: Estimated age-standardized incidence rate per 100,000 (Ovary, all ages)](image-url)
Clinical background of ovarian cancer

Only stage I of epithelial ovarian cancer is limited to the ovaries

Fig. 2: Carcinoma of the ovary. Staging ovarian cancer: primary tumor and metastases (FIGO and TNM)
1. Clinical background

Early diagnosis of epithelial ovarian cancer is still a big challenge

75 % of patients with EOC show symptoms only at later stages (stages III – IV). Most of these symptoms are rather vague like increases of the abdomen, pelvic abdominal pain, or urge to urinate. Often the disease has progressed at this point where there is a decreased survival rate.⁷

Survival rate in ovarian cancer patients is clearly dependent on the type and quality of surgery to remove the tumor as completely as possible. The highest survival rate can be achieved when treatment is done in centers specialized in gynecologic oncology.⁸

Improvement in 5-year disease free survival for EOC I patients was observed without tumor rupture during surgery compared with those with tumor rupture.⁹

Fig. 3: 5-year survival rate in ovarian cancer is dependent from stage. Graph adapted from Salani, R., et al. (2009)⁷

Fig. 4: Kaplan-Meier survival curve of women with progressive epithelial ovarian cancer after surgery depending on the type of treating physician. Graph adapted from Paulsen, T., et al. (2006)⁹
2. Importance of oncological biomarkers to support the early detection of ovarian cancer

The combination of HE4 and CA125 is more sensitive in detecting EOC than either marker alone

In a study by Moore et al., sensitivities of various oncological biomarkers were compared at different specificities in samples from 233 patients with 67 invasive ovarian cancers and 166 benign ovarian neoplasias.\textsuperscript{10}

- As a single tumor marker, HE4 had the highest sensitivity for detecting ovarian cancer, especially stage I disease
- The combination of CA125 and HE4 added 33.1% to the sensitivity of CA125 alone and 3.5% to the sensitivity of HE4 alone

![Fig. 5: Sensitivities of CA125 and HE4 at different specificities for differentiating benign disease from ovarian cancer (all stages) \textsuperscript{10}]

In a study by Montagnana et al., HE4 and CA125 values of patients with EOC in different stages were compared to a control group.\textsuperscript{11}

- CA125 showed a good discrimination between controls and cancer patients only in later stages
- HE4 showed a good discrimination between controls and cancer patients also in early stages
- Detection of early stages of ovarian cancer – where CA125 alone shows limited diagnostic performance – benefits from the supplementary use of HE4

![Fig. 6: Comparison of CA125 and HE4 in differentiating healthy women from women with early cancer stages. Graphs adapted from Montagnana, M., et al. (2009)\textsuperscript{11}]

\textsuperscript{10} In a study by Moore et al., sensitivities of various oncological biomarkers were compared at different specificities in samples from 233 patients with 67 invasive ovarian cancers and 166 benign ovarian neoplasias.\textsuperscript{10}

\textsuperscript{11} In a study by Montagnana et al., HE4 and CA125 values of patients with EOC in different stages were compared to a control group.\textsuperscript{11}
**HE4 helps to differentiate ovarian endometriotic cysts from ovarian cancer**

In a study by Huhtinen, K., et al. (2009), serum CA125 and HE4 concentrations of a control group were compared with patients with several stages of endometriosis, endometrial cancer (EmCa) and epithelial ovarian cancer (EOC).¹²

- CA125 can also be increased in endometriosis
- HE4 shows a better differentiation between cancer and endometriosis
- HE4 allows a better differentiation between benign and malignant diseases than CA125
- Both biomarkers together provide valuable information to discriminate ovarian malignancies from benign ovarian endometriotic cysts

Fig. 7: Comparison of CA125 and HE4 in differentiating various stages of endometriosis from ovarian cancer. Graph adapted from Huhtinen, K., et al. (2009)¹²
HE4 and CA125 can be combined in a mathematical algorithm to better assess the risk of EOC in women with a pelvic mass.

**Risk assessment with the ROMA score (risk of ovarian malignancy algorithm):**

The score is used to calculate the risk of having EOC in women arriving at the physician with a pelvic mass. It includes the biomarker levels of HE4 and CA125 and also considers the menopausal status of the woman.

The dual marker combination can be used to classify women into high and low risk groups allowing for the effective triage of women to appropriate surgical centers for their care.\(^\text{13}\)

### Pelvic mass: Risk of ovarian malignancy algorithm (ROMA)

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<tr>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
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<tr>
<td>(\text{PI} = -12.0 + 2.38 \ln(\text{HE4}) + 0.0626 \ln(\text{CA125}))</td>
<td>(\text{PI} = -8.09 + 1.04 \ln(\text{HE4}) + 0.732 \ln(\text{CA125}))</td>
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### ROMA-value [%] = \(\exp(\text{PI}) / [1 + \exp(\text{PI})] \times 100\)

\(\exp(\text{PI}) = e^\text{PI}\)

| <11.1% | ≥11.4% | <29.9% | ≥29.9% |
| low risk | high risk | low risk | high risk |

*Fig. 8: Calculation of the ROMA-values for pre- and post-menopausal women and individual cut-points for the Elecsys assays to separate between low and high risk patients*
The effectiveness of the Elecsys HE4 assay in combination with the Elecsys CA125 assay for risk estimation of EOC of patients presenting with pelvic mass was determined in an international multicenter clinical trial using repository samples. A total of 384 patient samples were included and the predictive probability for ovarian cancer as well as the ability for separation into a low and a high risk group based on ROMA values were determined. The cut-points above of 11.1% and 29.9% for pre- and post-menopausal women respectively were used in order to provide a specificity level of 75% for the Elecsys HE4 and Elecsys CA 125 assay combination.

- 94% of all women were classified correctly
- The sensitivity for stratifying patients with stage I-IV epithelial ovarian cancer into the high risk group was 84.3% at a specificity of 75%.
- The positive and negative predictive values were 64.9% and 90% respectively.
- AUC (95% CI):
  - Pre-menopausal woman = 0.858 (0.779–0.937)
  - Post-menopausal woman = 0.923 (0.885–0.962)

Fig. 9: ROC graph for ROMA using Elecsys HE4 and CA125 for pre- and post-menopausal women for differentiating benign diseases from ovarian cancer (all stages)
3. The clinical value of HE4 in disease monitoring and follow-up

The combined use of HE4 and CA125 has a significant predictive value

The combination of HE4 and CA125 appears to have a significant value in predicting optimal surgical outcome and development of resistant disease in platinum-based chemotherapy treated EOC patients. Elevated plasma levels 6 months after 1st line chemotherapy significantly correlate with overall and progression-free survival in platinum-sensitive patients.13

HE4 supports CA125 to better monitor ovarian cancer

In addition to the use of HE4 and CA125 for the risk stratification of women with a pelvic mass, HE4 can be used to monitor the disease status in ovarian cancer patients. Both biomarkers CA125 and HE4 are of complementary nature. While in most of the cancer patients both markers are expressed in significant amounts, there are patients who are positive for only one of the biomarkers HE4 and CA125. Thus the combined use of CA125 and HE4 could facilitate the detection of recurrent disease by reducing the number of biomarker negative patients and delivering more confidence when both markers show increasing values.

The use of HE4 during primary chemotherapy of EOC was evaluated by Hynninen, J., et al. (2011) and it could be shown that the profile of HE4 during primary chemotherapy was in line with radiologic and clinical responses. In the neoadjuvant chemotherapy group, HE4 correlated better with the radiologic response than CA 125.16

The effectiveness of the Elecsys HE4 assay as an aid in monitoring of disease status in ovarian cancer patients was determined by assessing changes in HE4 levels in serial serum samples from 100 patients compared to changes in disease status. A study involving a total of 375 pairs of observations was undertaken with ≥ 3 blood withdrawals per patient.

A change in HE4 concentration of > 20 percent suggested recurrence or disease progression, while a decrease of this magnitude suggested therapeutic response.14
Benefits of HE4 and CA 125

• Reduction of biomarker-negative ovarian carcinomas
• Improves risk stratification of pelvic mass patients and triage to specialists
• Higher sensitivity of HE4 improves early diagnosis of EOC
• Detects recurrence earlier
References

15. Braicu, I., Cherekov, R., Richter, R., Vergote, I.B., et al. (2012). Use of HE4 and CA125 to predict surgical outcome and for prognostic value for progression-free survival (PFS) and overall survival (OS) in primary epithelial ovarian cancer (EOC) patients (pts). J Clin Oncol 30 (suppl; abstr 5034).

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