HE4 AS A BIOMARKER FOR OVARIAN CANCER: A CRITICAL REVIEW

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INTRODUCTION

Ovarian cancer (OC) is a common malignant disease and represents the primary cause of death from gynecological cancers. According to estimates made by the American Cancer Society, during 2014 about 21,980 women in the United States will receive new diagnosis of OC and about 14,270 women will die from OC. Overall, the 5-year survival rate is relatively low, less than **30%**. This is due to the delayed diagnostic of OC, when it is already in advanced stages (Fig. 1: stages III-IV). Due to OC not having symptoms in early stages, tumoral biomarkers are becoming an important and significant tool for early identification of OC, detection of recurrence and monitoring of response to therapy. Currently, the serum marker carbohydrate antigen 125 (**CA125**) is the most widely used tumour marker in OC. Nevertheless, levels of CA125 are elevated in less than 50% of early-stage OC cases, and are also high in different benign gynecologic diseases. This results in a reduction of sensitivity and specificity and the need of a novel biomarker research. In 1991, the human epididymis protein (**HE4**) was discovered by Kirchoof et al. Eight years later was described as an OC biomarker. The aim of the present review is to assess the different aspects of HE4 as a biomarker of OC.
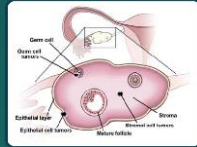
Figure 1: Ovarian Cancer staging by International Federation of Gynecology and Obstetrics criteria (2002) (1).

Figure 2: Ovarian cancer types (2).

METHODOLOGY

This section includes a briefly summary about methodology followed on analyzed papers as well as the most relevant algorithms for OC diagnose.

1 **Study population:** patients are needed for carrying out an investigation. Different cohorts were enrolled in the investigation.

2 **Levels of biomarker:** biomarkers are an interesting tool for diagnose confirmation: they have a high pronostic value in diagnostic, they allow a monitoring of the treatment efficacy and they can detect recurrences.

3 **Statistical analysis:** all data was analyzed using different statistics programs. For all analyses, a P-value of <0.05 was considered as statistically significant.

Risk of malignancy index (RMI)
It is a simple scoring system based on menopausal status, ultrasound scan and serum concentrations of CA125.

Risk of ovarian malignancy algorithm (ROMA)
ROMA combines the diagnostic power of the CA125-HE4 marker panel with menopausal status.

RESULTS

This part of the poster will be focused on the **Objectives** of the paper. Thus, a division of this section in squares will be made to relate each aim to its results.

The role of HE4 (WDFD2) in OC
Little is known about the function of HE4 gene or the role the gene products plays. Moore and colleagues demonstrated the impact of HE4 overexpression on OC proliferation. They developed stable HE4 overexpressing SKOV-3 and OVCAR-8 OC cell clones. Indeed, they showed that antisense inhibition of HE4 via novel PTOs resulted in reduced OC cell viability and supressed growth of xenografted tumors in mice.
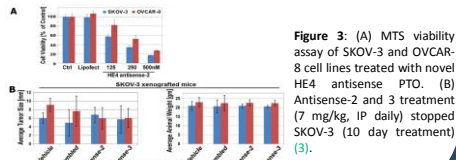
Figure 3: (A) MTS viability assay of SKOV-3 and OVCAR-8 cell lines treated with novel HE4 antisense PTO. (B) Antisense-2 and 3 treatment (7 mg/kg, IP daily) stopped SKOV-3 (10 day treatment) (3).

Correlation between: the HE4 levels and the survival rate, the HE4 levels with the tumor stage and chemotherapeutic treatment and levels of HE4
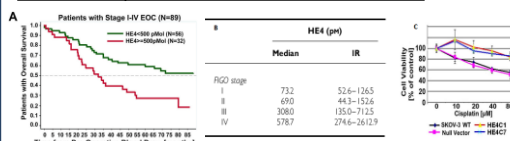
Figure 4: (A) Kaplan-Meier survival curve of 89 patients (3). (B) HE4 levels according to FIGO stage (4). (C) MTS based cell viability related with cisplatin treatment of 24h (3).

HE4 as a biomarker of other types of cancer
The literature confirmed HE4 as a biomarker for endometrial cancer. New insights suggested HE4 as a biomarker for heart failure, lung cancer and renal fibrosis.

Factors to consider in HE4 levels measurement
HE4 is not expressed in mucinous OC. In pregnant women the levels of HE4 are decreased. Serum levels of HE4 are increased with age. Women with later menarche and smokers also had significantly higher levels of HE4.
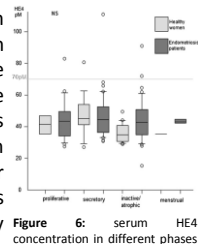
Figure 6: serum HE4 concentration in different phases of the menstrual cycle (5).

Comparison between CA125 and HE4
Serum HE4 levels were less frequently elevated than CA125 levels in women with benign gynecologic disorders (8% vs 29%).
Indeed, the diagnostic performance of serum HE4 was superior to that of CA125, particularly for early stages' (I-II) patients.

	HE4		CA125	
	Sensitivity %	Specificity (%)	Sensitivity (%)	Specificity (%)
Ferraro et al	79	93	79	78
Yang et al	73	89	-	-
Moore et al	72.9	95	61.2	90
Jinping et al	68.5	87.6	-	-
Holcomb et al	64.7	91.8	85.3	59.5
Molina et al	79.3	98.9	82.9	70.9
Montagnana et al	76.4	93.9	70.9	77.6
Van Gorp et al	74.5	83.3	79.5	81.6
A. Lowe et al	78.1	86.3	84.4	67.4

Figure 5: Diagnostic performance of HE4 and CA125.

The use of HE4 alone or with other biomarkers
In combination, HE4 and CA125 achieved the highest sensitivity for detecting invasive epithelial OC of 76,4% at a set specificity of 95% of all the biomarkers.

CONCLUSIONS

- HE4 expression is a molecular factor in ovarian cancer tumorigenesis.
- Levels of HE4 are inversely related to overall survival and chemoresistance; and directly related to FIGO stages.
- In an overall vision, HE4 outperforms CA125 as a biomarker for OC.
- The combination of HE4 and CA125 may be a better predictor of malignancy than either marker alone in pelvic masses and ovarian endometriotic cysts.
- When measuring HE4 levels, a variety if factors should be carefully considered: HE4 is not expressed in mucinous OC, in pregnancy HE4 levels are decreased, serum levels of HE4 are increased with age and in some conditions, such as renal failure, HE4 levels are elevated.

References

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