



## **Human epididymal protein 4**

*The role of HE4 in the management of patients  
presenting with pelvic mass*

*Publication abstracts*



Ovarian cancer is diagnosed annually in more than 200,000 women worldwide, with the greatest incidence in the US and Northern Europe, and lowest incidence in Africa and Asia.

It is the fourth leading cause of cancer death worldwide and is responsible for 5% of all cancer deaths in women. However, fewer than 30% of all ovarian cancers are diagnosed in stages I/II and worldwide mortality from ovarian cancer has decreased only by 12% since 1973.

Less than half of ovarian cancer patients have their diagnostic surgery with a gynaecologic oncologist trained in the management of ovarian cancer which can cause further reduction in survival rates. (Data from cancer epidemiology database: <http://www-dep.iarc.fr/>)

**The assay combination of HE4 and CA 125 can be used to guide patients to the appropriate specialist.**

# The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma

The WFDC2 (HE4) gene is amplified in ovarian carcinomas, whereas its expression in normal tissues, including ovary, is low. Although the function of the HE4 protein is unknown, it is a member of a family of stable 4-disulfide core proteins that are secreted at high levels.

Blinded studies on sera from postmenopausal patients with ovarian carcinoma and controls indicate that the specificity and sensitivity of the HE4-based ELISA is equivalent to that of the CA 125 assay. However, the HE4 assay may have an advantage over the CA 125 assay in that it is less frequently positive in patients with nonmalignant disease.

*I. Hellström et al.  
The HE4 (WFDC2)  
protein is a biomarker  
for ovarian carcinoma  
Cancer Research 2003,  
63, 3695-3700.*

# Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas

In comparison with normal surface epithelium, which does not express HE4, we found that cortical inclusion cysts lined by metaplastic Mullerian epithelium abundantly express the protein. Its expression in tumors was restricted to certain histologic subtype: 93% of serous and 100% of endometrioid epithelial ovarian cancers expressed HE4, whereas only 50% and 0% of clear cell carcinomas and mucinous tumors, respectively, were positive. Tissue microarrays revealed that the majority of nonovarian carcinomas do not express HE4, consistent with our observation that HE4 protein expression is highly restricted in normal tissue to the reproductive tracts and respiratory epithelium.

*R. Drapkin et al.  
Human epididymis  
protein 4 (HE4) is a  
secreted glycoprotein  
that is overexpressed  
by serous and  
endometrioid ovarian  
carcinomas.  
Cancer research 2005,  
65, 2162-2169.*

## **As a single tumor marker, HE4 had the highest sensitivity for detecting ovarian cancer, especially stage I disease. Combined CA 125 and HE4 is a more accurate predictor of malignancy than either marker alone**

Two hundred and fifty-nine patients with adnexal masses were enrolled. Of these, 233 patients were eligible for analysis with 67 invasive epithelial ovarian cancers and 166 benign ovarian neoplasms. Mean values for all marker levels except Her2 differed significantly between patients with benign masses and cancer. As a single marker, HE4 had the highest sensitivity at 72.9% (specificity 95%). Comparatively, combined CA 125 and HE4 yielded the highest sensitivity at 76.4% (specificity 95%), with additional markers adding minimally to the sensitivity of this combination. HE4 was the best single marker for Stage I disease, with no increase in sensitivity when combined with CA 125 or any other marker.

*R.G. Moore et al.  
The use of multiple  
novel tumor biomarkers  
for the detection of  
ovarian carcinoma in  
patients with a pelvic  
mass.  
Gynecologic Oncology  
2008, 108, 402-408.*

# HE4 represents the first novel biomarker that complements CA 125 measurement in patients with ovarian cancer by providing improved sensitivity at fixed levels of specificity

Early studies on CA 125 demonstrated that the sensitivity is approximately 80% at the Upper Limit of Normal of 35 U/mL. The study by Moore et al. showed that CA 125 + HE4 provided a sensitivity of 81%, compared to 61.2% for CA 125 alone, at 90% specificity. In addition, Brown et al. demonstrated that of the approximately 20% of ovarian cancer patients that had negative CA 125 measurements, almost half had elevated concentrations of HE4.

*J.W. Allard et al.  
HE4 and CA125  
combined for the  
improved management  
of ovarian cancer  
Oncology 2009, 3,  
20-21.*

# Discrimination of ovarian tumors from ovarian endometriotic cysts can be done by measuring HE4 and CA 125 in serum

Human epididymis secretory protein E4 (HE4, also known as WAP four-disulphide core domain protein 2) is a new promising biomarker for ovarian cancer but its specificity against ovarian endometriotic cysts is only superficially known. Serum HE4 concentrations together with CA 125 were analysed in serum samples of women diagnosed with various types of endometriosis, endometrial cancer or ovarian cancer, and in samples from healthy controls.

The mean serum concentration of HE4 was significantly higher in serum samples of patients with both endometrial (99.2 pM,  $P < 0.001$ ) and ovarian (1125.4 pM,  $P < 0.001$ ) cancer but not with ovarian endometriomas (46.0 pM) or other types of endometriosis (45.5 pM) as compared with healthy controls (40.5 pM).

The serum CA 125 concentrations were elevated in patients with ovarian cancer, advanced endometriosis with peritoneal or deep lesions, or ovarian endometriomas, but not in the patients with endometrial cancer.

*K. Huthinen et al.  
Serum HE4  
concentration  
differentiates  
malignant ovarian  
tumours from ovarian  
endometriotic cysts.  
British J. Cancer 2009,  
100, 1315-1319.*

## **HE4 is elevated in all stages of endometrial cancer and is more sensitive in early-stage endometrial cancer compared to CA 125**

Serum samples from 156 healthy subjects and 171 patients with endometrial cancer (122 stage I, 17 stage II, 26 stage III, and 6 stage IV) were analyzed. At a 95% specificity, the sensitivities for differentiating between healthy subjects and all stages of cancer were 45.5% for HE4 and 24.6% for CA 125. For stage I disease, HE4 yielded a 17.1% improvement in sensitivity compared with CA 125.

*R.G. Moore et al.  
Utility of a novel serum  
tumor biomarker  
HE4 in patients  
with endometrial  
adenocarcinoma of the  
uterus.  
Gynecologic oncology  
2008, 110, 196-201.*



# The dual marker combination of HE4 and CA 125 in a risk of malignancy algorithm can be used to classify women into high and low risk groups

The addition of HE4 to CA 125 enables the detection of malignancies in patients with tumors that do not express CA 125 and will be missed by algorithms that employ CA 125 alone. Equally important, a combination of HE4 and CA 125 or HE4 alone has been shown to have greater sensitivity in patients with early stage disease compared with CA 125.

In a trial, twelve sites enrolled 531 evaluable patients with 352 benign tumors, 129 EOC, 22 LMP tumors, 6 non EOC and 22 non ovarian cancers. The postmenopausal group contained 150 benign cases of which 112 were classified as low risk giving a specificity of 75.0% (95% CI 66.9–81.4), and 111 EOC and 6 LMP tumors of which 108 were classified as high risk giving a sensitivity of 92.3% (95% CI=85.9–96.4). The premenopausal group had 202 benign cases of which 151 were classified as low risk providing a specificity of 74.8% (95% CI=68.2–80.6), and 18 EOC and 16 LMP tumors of which 26 were classified as high risk, providing a sensitivity of 76.5% (95% CI=58.8–89.3).

*R.G. Moore et al.  
A novel multiple  
marker bioassay  
utilizing HE4 and  
CA 125 for the  
prediction of ovarian  
cancer in patients with  
a pelvic mass.  
Gynecologic Oncology  
2009, 112, 40-46.*

# Conclusions from publications

- When diagnosed at an early stage, ovarian cancer and endometrial carcinoma patients tend to have good prognoses. Late-stage detection of either malignancy, however, typically translates into a poor prognosis. An accurate biomarker for early detection of these diseases is, thus, urgently needed.
- Multiple putative markers for ovarian and endometrial cancer have been discovered. Only a handful have been tested in a sufficient number of patients. One protein, the human epididymis protein (HE4), has shown a strong potential for clinical application.
- Combining the use of HE4 with CA 125 has improved diagnostic specificity by excluding some benign conditions.
- HE4 can be used for stratification of patients with a pelvic mass. Proper triage of patients using HE4 may control costs associated with evaluation of pelvic masses.
- In the future, HE4 may be a component of serum screening test for ovarian or endometrial cancer.

# Roche Elecsys HE4\* and Elecsys CA 125

A fully automated assay used for the quantitative determination of HE4 in human serum and plasma as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer.

It is further intended to be used in conjunction with the Elecsys® CA 125 II as an aid in estimating the risk of epithelial ovarian cancer in premenopausal and postmenopausal women presenting with pelvic mass.

## Technical assay features of HE4\* and CA 125

	HE4	CA 125
Total duration	18 min.	
Assay principle	Immunoassay based on ECLIA	
Sample volume	10 µL	20 µL
Sample material	Serum and plasma	
Measuring range	15 - 1,500 pmol/L	0.6 - 5,000 U/mL
Analytical sensitivity	5 pmol/L	0.6 U/mL
Traceability	HE4 EIA of Fujirebio Diagnostics, Inc.	Enzymun-Test CA 125 II method, which in turn has been standardized against the CA 125 II RIA from Fujirebio Diagnostics, Inc.
Kit size	100 determinations	

\* Currently in development. Launch in February 2011.

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Roche Diagnostics Ltd.  
CH-6343 Rotkreuz  
Switzerland  
[www.cobas.com](http://www.cobas.com)