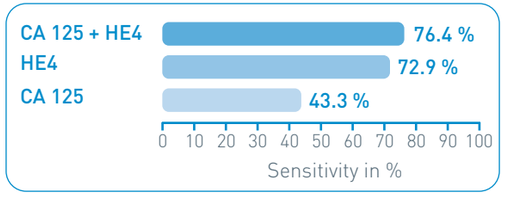
HE4 : Human Epididymis-specific protein 4

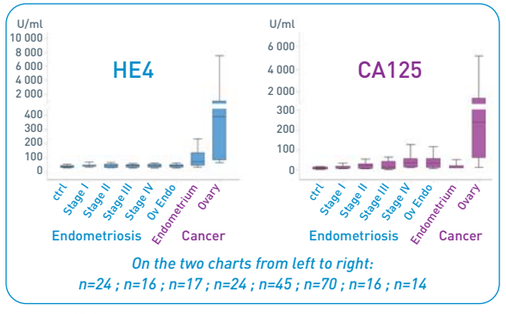
HE4 is an epididymis protein known since 1991. Since 1999, over expression was identified in patients suffering from first stages of ovarian cancer (stages I and II) and mainly found in cases of serous cancers. Its expression is independent of CA125 and it is effective in 50% of cancers which do not express CA125.

The HE4 protein offers better sensitivity and specificity than CA125.
Its combination with serum markers improves the sensitivity and specificity of ovarian cancer detection in the early stages as well as in cases of relapse.



Sensitivity for the detection of ovarian cancers in patients with a pelvic mass (95% specificity; pre and post menopausal combined)

HE4 is more specific than CA125 and permits the differential diagnosis of endometriosis to be made.



On the two charts from left to right:
n=24 ; n=16 ; n=17 ; n=24 ; n=45 ; n=70 ; n=16 ; n=14

Differential diagnosis of endometriosis

The HE4 protein marker is not totally specific to ovarian tissue, or ovarian cancer: it is over-expressed in thyroid cancers, pulmonary adenocarcinomas, mammary adenocarcinomas and mesotheliomas.

ROMA: Risk of Ovarian Malignancy Algorithm

The ROMA algorithm assesses the risk of malignancy by combining the serum HE4 result, the CA125 result and the menopausal status.

It allows patients to be classed according to their risk of malignancy level, i.e. low or high.

Interpretation*

In pre-menopausal women:

- ROMA ≥ 11.4 = high risk of ovarian cancer
- ROMA < 11.4 = low risk of ovarian cancer

In post-menopausal women:

- ROMA ≥ 29.9 = high risk of ovarian cancer
- ROMA < 29.9 = low risk of ovarian cancer

In a multicentric study that included 457 women presenting with a pelvic mass, the ROMA algorithm allowed an ovarian epithelial cancer to be distinguished from a benign tumour in 94.3% of patients, and notably to identify 85.3% of stage I and stage II cases**.

**Method used ECL Roche: the ROMA risk can only be calculated by combining CA125 and HE4 in the same technological method.*

***Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay vs. the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol 2010;203:208.e1-6.*

Clinical interest of the HE4 marker and ROMA

Assistance in the early diagnosis of epithelial ovarian cancer (stages I and II) and the detection of relapses

- The implementation of treatment as quickly as possible and at an early stage
- Increased survival rate

Better risk staging in patients with a pelvic mass or an ovarian cyst

- Exclusion of a malignant tumour or rapid orientation towards a multidisciplinary and specialised team
- Reduction of unnecessary surgical interventions

In practice

Test request

HE4* + CA125 *+ score ROMA
The ROMA malignancy risk calculation integrates the HE4 result, CA125 result and the menopausal status of the patient.

Please indicate: whether the patient is pre-menopausal or menopausal.

**HE4 and CA125 are measured using the same technology, which does not authorise the integration of a transferred CA125 result*

Sample

- 1mL of serum
- Minimum quantity: 600 µL
- The serum must be separated from the blood cells then frozen at -20°C.

To find out more about this subject

Find all the necessary details at:
www.biomnis.com › Test Menu › Test guide or use the Biomnis mobile application
BIOMNIS group code: HE4

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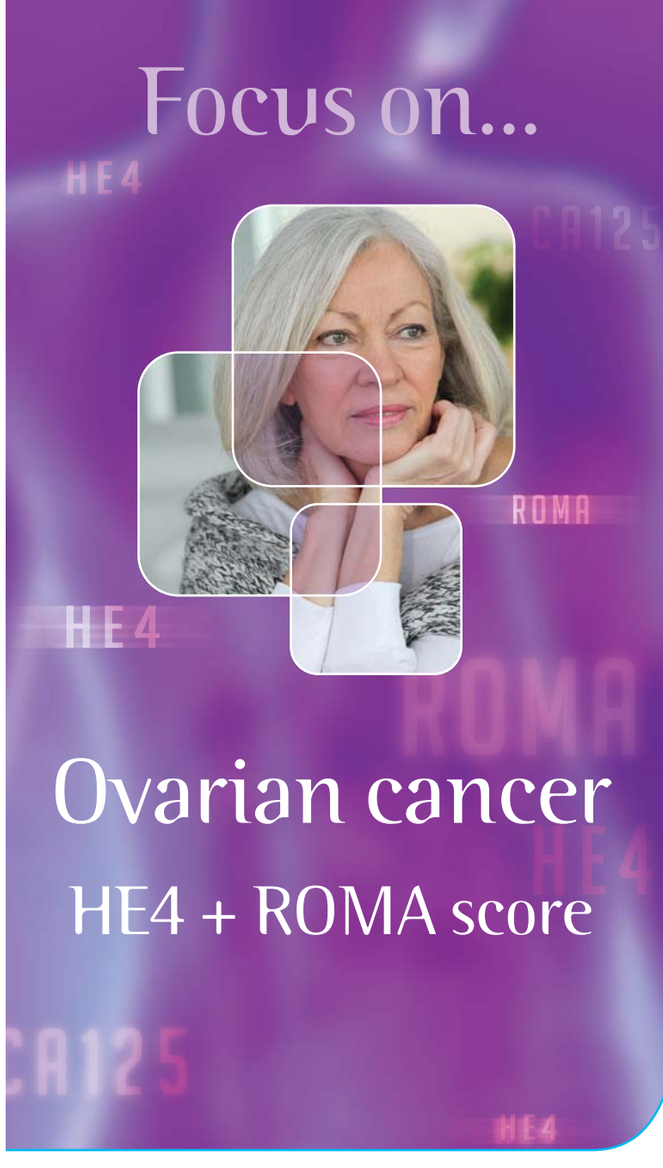


NOVEMBER 2013

biomnis
SPECIALISED MEDICAL PATHOLOGY

*Ovarian cancer in the world**

225,000 new cases
of ovarian cancer

Accounting for around 4%
of all cancers diagnosed in women

Incidence rates vary considerably across the world, with World age-standardised rates in more developed countries being **nearly twice as high as** those in less developed countries

The estimated World age-standardised incidence rate for the more developed regions of the world was **9 per 100,000**, and 5 per 100,000 for the less developed countries.

Numerous women are involved in a suspected case of ovarian cancer.

The symptoms are non-specific and are of late-onset in this type of cancer.

AIMS

- Establish an early diagnosis
- Determine the stage of the disease
- Screen for the risk factors

Provide multidisciplinary and rapid care

**Source: Cancer Research UK (2008 data)*

The diagnosis

The diagnosis relies on the medical background, the clinical examination and medical imaging (ultrasound and MRI).

The definitive diagnosis of cancer is made through anatomical pathology investigations and requires a histology sample to be taken.

When confronted with a diagnosis of epithelial ovarian cancer, screening for the BRCA1 or 2 mutation is strongly advised*.

Medical background

Screening for risk factors, notably a personal and familial history of cancer and comorbidities.

Risk increases

- Age
- Caucasian population
- Late menopause
- BRCA gene mutations: BRCA1 (risk increases by 60-fold), BRCA2 (30-fold)
- Nulliparity, infertility, endometriosis

Risk decreases

- History of hysterectomy
- Oral contraception
- Multiparity

**Source : NCCN Guidelines Version 4.2013. Hereditary Breast and/or Ovarian Cancer Syndrome*

Clinical and complementary investigations

Pelvic mass
Abdominal distension
etc.

No specific or early symptoms:
abdominal pain, fatigue etc.

- Family history
- Abdominal examinations / pelvic examinations
- CA125 + HE4
- Ultrasound scan
- CT scan
- Radiography
- Gastro-intestinal investigation
- Full blood count
- Biochemistry

Transvaginal ultrasound:
Confirmation of the ovarian origin

Exploratory surgery
Histology

Malignant | **Benign**

The initial pre-treatment dose for the CA125 marker is recommended.

The assays for markers CA 19-9 and CAE are only performed if clinically or radiologically indicative of an ovarian mucinous tumour or suggestive of a differential diagnosis of a digestive tumour.

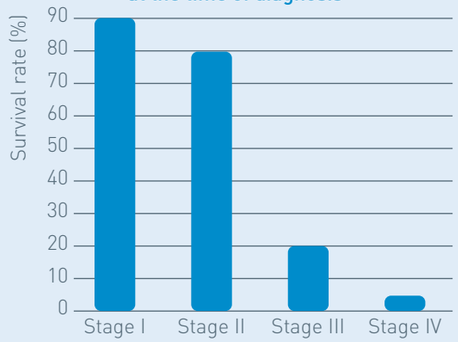
The prognosis

It is essential to determine the disease stage at the time of diagnosis.

Survival at 5 years of ovarian cancer:

75 - 95% if the cancer is located in the ovaries
10 - 17% if metastasis has occurred
30% all stages grouped together

The survival rate relative to the stage at the time of diagnosis



Other factors influencing the prognosis:
age, comorbidities, histology results, the grade and presence of a residual tumour following surgery.

Relapses
The risk of a relapse at 5 years is 80%.
The majority of relapses appear in the first three years of treatment.
Early onset relapses have a poor prognosis.

Early diagnosis and the detection of relapses is the only way to improve the short-term prognosis.