INTRODUCTION

Ovarian cancer is the most lethal malignancy of gynecological origin. Cancer in the ovary may derive from epithelium (95% cases) or stromal supporting cells or germ cells. The most common ovarian epithelial malignancies are Serous tumors (50%); Mucinous tumors (25%); Endometrioid carcinoma (15%); Clear cell carcinoma (5%); Brenner tumor (1%). CA 125 is a marker of epithelial ovarian malignancy.

NORMAL RANGE

<35.0 U/mL

CLINICAL USE

- An aid in the management of Ovarian cancer patients. Preoperative CA 125 level of < 65 U/mL is associated with a significantly greater 5 year survival rate.
- Monitor the course of disease in patients with Invasive epithelial ovarian cancer
- Detection of residual tumor in patients with Primary epithelial ovarian cancer who have undergone first line therapy. Persistent elevation of CA 125 levels after 3 cycles of therapy indicates a poor prognosis.

<table>
<thead>
<tr>
<th>STAGE OF OVARIAN CANCER</th>
<th>PERCENTAGE POSITIVITY OF CA 125</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>50</td>
</tr>
<tr>
<td>Stage II</td>
<td>90</td>
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<tr>
<td>Stage III &amp; IV</td>
<td>&gt;90</td>
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INTERPRETATION

Increased Levels

| Malignant disease | Non mucinous epithelial ovarian carcinoma (85%)
|                  | Fallopian tube tumors (100%)
|                  | Cervical adenocarcinoma (83%)
|                  | Endometrial adenocarcinoma (50%)
|                  | Squamous cell carcinoma cervix / vulva (15%)
|                  | Trophoblastic tumors (45%)
|                  | Non-Hodgkin lymphoma (40%)
|                  | Cancer of Pancreas / Liver / Lung

| Endometrial conditions | Pregnancy (27%)
|                       | Endometriosis
|                       | Menstruation

| Pleural effusion | Cancer
|                 | Congestive heart failure
<table>
<thead>
<tr>
<th>Peritoneal effusion</th>
<th>Pelvic inflammatory disease</th>
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<tbody>
<tr>
<td></td>
<td>Bacterial peritonitis</td>
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<tr>
<td>Non malignant conditions</td>
<td>Cirrhosis (66%)</td>
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<tr>
<td></td>
<td>Disorders of GIT / Liver / Pancreas</td>
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<td></td>
<td>Renal failure</td>
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<tr>
<td>Healthy individuals</td>
<td>1%</td>
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**Decreased Levels**

- Postmenopausal women
- African American & Asian women have lower normal values

**HIGH RISK FACTORS FOR OVARIAN CANCER**

- Epidemiologic factors – increasing age specially above 60 years. Females have approximately 1:72 lifetime risk of developing ovarian cancer.
- Genetic factors – 10% women with ovarian cancer have a somatic mutation in BRCA1 or BRCA2 & Lynch syndrome Type II caused by mutations in repair genes (MSH2, MLH1, MLH6, PMS1 & PMS2)
- Nulliparity
- Use of talc agents to the perineum
- Obesity
- Hormone Replacement Therapy (HRT)

**PROTECTIVE FACTORS FOR OVARIAN CANCER**

- Oral contraceptives
- Multiparity
- Breast feeding
- Fallopian tube ligation

**EARLY DETECTION OF OVARIAN CANCER**

- CA125 is recommended along with Transvaginal ultrasound (TVS) for early detection of ovarian cancer in women with hereditary syndromes.
- It also acts as an adjunct in distinguishing benign from malignant suspicious pelvic masses in postmenopausal women.

**LABORATORY DIAGNOSIS**
Diagnosis of ovarian cancer is made on **histological examination** of tissue or **cytology** of peritoneal or pleural fluid if present. Rarely abnormal glandular cells may be seen on Pap smear which on further workup are found to originate from the ovary.

Imaging for identifying an adnexal mass

**Blood biomarkers** –

- CA125 – CA125 is elevated in approximately 50% patients with early stage disease and >80% patients with advanced disease. Thus serial CA125 levels over time may be beneficial as a screening tool.
- Human epididymis protein 4 (HE4) – helpful in diagnosing recurrent or progressive disease or in the evaluation of a suspicious adnexal mass. This is an FDA approved test for monitoring the disease.
- ROMA (Risk of ovarian malignancy algorithm) – it is used as a supplement to the standard pre-surgical evaluation of a patient with a pelvic mass to assess likelihood of malignancy prior to surgery specially in those cases where presurgical evaluation does not indicate malignancy.
- Carcinoembryonic antigen (CEA) – non specific marker as it is elevated in non malignant conditions also
- OVA1 – is a panel of 5 serum biomarkers of which 2 markers are up-regulated (CA125 & Beta 2 microglobulin) & 3 markers are down-regulated (Transferrin, Transthyretin & Apolipoprotein A1). An algorithm determines the patients risk for ovarian cancer

**LIMITATIONS**

- CA125 level is not increased in Mucinous adenocarcinomas.
- Normal concentration of CA125 does not exclude presence of the tumor.
- Even at high concentrations, CA125 alone is not useful for distinguishing benign from malignant pelvic masses.
- Although CA125 may be increased 12 months before clinical evidence of disease, it is not recommended for screening women for Serous carcinoma ovary because it is not increased in 20% cases at the time of diagnosis and in <10% cases with Stage I / II carcinoma.
- In postoperative monitoring cases for persistent / recurrent disease, 95% patients show CA125 >35 U/mL but a negative result does not exclude residual disease.
- In 0.6% of normal women >50 years of age, CA125 levels may be increased
- Rising level of CA125 during chemotherapy is associated with tumor progression and return to normal is associated with a good response. However it may remain elevated in stable or progressive Serous carcinomas.
- Different assays do not produce equivalent values and should not be used interchangeably.