Ovarian Cancer
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Introduction

- Ovarian cancer accounts for 3–4% of cancer in women
- And is the fourth most frequent cause of cancer-related death in females in the United States
- In the year 2005, an estimated 22,000 new ovarian cancer cases were diagnosed in the United States and 16,000 patients succumbed to the disease.
- Ovarian cancer is the second most common gynecologic malignancy, endometrial cancer being the most common, but is the most common cause of death among women who develop a gynecologic malignancy.
- In general, ovarian cancer is a disease of the postmenopausal woman, with the highest incidence among patients ages 65–74 year.
Risk Factors

- Family History
- Ethnicity
- Reproduction
- Others
The strongest risk factor

A women with a single first-degree relative with ov.Ca has a relative risk (RR) of approximately 3.6 for developing ov.ca compared with general population

Her lifetime risk approx. 5%

5-10% of ov.ca are linked to identifiable, inherited mutations in certain genes

Families in which three or more first-degree relatives have ovarian or ovarian plus breast cancer are likely to have a cancer-susceptibility genetic mutation that is transmitted in an autosomal-dominant inheritance pattern
Three familial ovarian cancer syndromes:

1. The site specific ovarian ov.ca syndrome
   - only ov.ca is seen
   - account for 10-15% of hereditary ov.ca.

2. The hereditary breast/ovarian cancer syndrome
   - associated with 65-75% of hereditary ov.ca.

3. The hereditary nonpolyposis colorectal cancer syndrome (HNPCC), affected individuals may have colon, endometrial, breast, ovarian or other cancers
Ethnicity

- Higher in white women
- Higher in north America and northern Europe than Japan
- Difference related to genetics, diet, or environmental exposure or a combination
- BRCA1 and BRCA2 genes are more common among white women of Ashkenazi descent
- Incidence of ov.ca is higher in countries with higher per capita consumption of animal fat
Reproduction factors

- Nulliparous
- First childbirth after age 35 years
- Involuntary infertility
- Late menopause and early menarche
- Pts. With prolonged period or uninterrupted ovulation
Others

- **Exogenous hormones** :- HRT
- **Dietary factors** , Diets high in saturated animal fats seem to confer an increased risk by unknown mechanisms ...

Japanese women who move to the United States have an increased ovarian cancer risk.

# Japanese women who move to the United States have an increased ovarian cancer risk.
Protective Factors

- Multiparity: First pregnancy before age 30
- Oral contraceptives: 5 years of use cuts risk nearly in half
- Tubal ligation
- Hysterectomy
- Bilateral oopherectomy
- Lactation
- Epidemiologic and laboratory evidence suggest a potential role for retinoids, vitamin D, NSAIDs as preventive agents for ovarian cancer
Ovarian cancer can be divided into three major categories based on the cell type of origin.

The ovary may also be the site of metastatic disease by primary cancer from another organ site.

Unlike carcinomas of the cervix and endometrium, precursor lesions of ovarian carcinoma have not been defined.
Pathology

- Major Histopathologic Categories of Ovarian Cancer

1- Epithelial
Serous, mucinous, endometrioid, clear cell, transitional cell (Brenner), undifferentiated

2- Germ Cell
Dysgerminoma, endodermal sinus tumor, teratoma (immature, mature, specialized), embryonal carcinoma, choriocarcinoma, gonadoblastoma, mixed germ cell, polyembryona

3- Sex Cord and Stromal
Granulosa cell tumor, bibroma, thecoma Sertoli-Leydig cell, gynandroblastoma
Pathology

- Major Histopathologic Categories of Ovarian Cancer

4- Neoplasms Metastatic to the Ovary

Breast, colon, stomach, endometrium, lymphoma
Pathogenesis

- Ovarian carcinogenesis can be divided into two broad phases:

  1- malignant transformation
  Benign \( \rightarrow \) borderline \( \rightarrow \) malignant ovarian tumors.

  2- peritoneal dissemination

** Now do not appear to be valid for the majority of ovarian cancers
Pathogenesis

New model of ovarian carcinogenesis:
Surface epithelial tumors divides into two broad categories: Type I and Type II
based on their clinico-pathologic features and characteristic molecular genetic changes
## Pathogenesis

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
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<tbody>
<tr>
<td>Low grade</td>
<td></td>
<td>High grade</td>
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<tr>
<td>Arise from precursor lesion in a stepwise fashion</td>
<td>- Cystadenoma</td>
<td>Arise “de novo”</td>
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<tr>
<td></td>
<td>- Borderline tumor</td>
<td></td>
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<tr>
<td>Typically present in stage I</td>
<td></td>
<td>Typically present in advanced stage</td>
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<tr>
<td>Slow growing, indolent</td>
<td></td>
<td>Rapid growing, aggressive</td>
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<tr>
<td>Often remains low grade</td>
<td></td>
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<tr>
<td>E.g.</td>
<td>Low grade micropapillary</td>
<td>E.g.</td>
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<tr>
<td></td>
<td>Mucinous</td>
<td>High grade serous</td>
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<td></td>
<td>Clear cell</td>
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<tr>
<td></td>
<td>endometroid</td>
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Diagnosis and Clinical Evaluation

- Ovarian cancer typically develops as an insidious disease, with few warning signs or symptoms. Most neoplastic ovarian tumors produce few symptoms until the disease is widely disseminated throughout the abdominal cavity.

- A history of **nonspecific gastrointestinal complaints**, including: nausea, dyspepsia, and altered bowel habits, is particularly common

- **Abdominal distention** as a result of ascites are generally signs of advanced disease.

- A change in **bowel habits**, such as constipation and decreased stool caliber, is occasionally noted. Large tumors may cause a sensation of pelvic weight or pressure.
Rarely, an ovarian tumor may become incarcerated in the cul-de-sac and cause severe pain, urinary retention, rectal discomfort, and bowel obstruction.

Menstrual abnormalities may be noted in as many as 15% of reproductive-age patients with an ovarian neoplasm.

Vaginal bleeding may occur in patients with ovarian cancer in the presence of a synchronous endometrial carcinoma or as a consequence of metastatic disease to the lower genital tract.

Ovarian stromal hyperplasia or hyperthecosis also may be associated with excess androgen production, which alters the normal menstrual cycle.
Diagnosis and Clinical Evaluation

- On Physical Examination

  1. General examination
  2. Abdominal examination:

     - Abdominal distention is one of the more common findings. The presence of flank fullness and shifting dullness implies the presence of ascites or a large pelvic-abdominal mass. Recent eversion of the umbilicus
  3. Lymph Node examination:

     - the supraclavicular and inguinal areas, Sister Mary Joseph's nodule refers to a metastatic implant in the umbilicus.
Diagnosis and Clinical Evaluation

- On Physical Examination,

4. Pelvic examination: A careful and thorough pelvic examination provides many helpful clues regarding the etiology of a pelvic mass.

# Benign mass: Mobile, smooth, cystic, unilateral
# Malignant mass: fixed, irregular, solid or firm, bilateral.

- If I find a mass .... What could be else !!!!

Endometrioma, Fibroid, Functional cyst, Ectopic pregnancy, Dermoid tumor (younger women)
Diagnosis and Clinical Evaluation

- **Investigations**, 

**Tumor Markers** :-

an antigenic determinant on a high-molecular-weight glycoprotein recognized by the murine monoclonal antibody OC-125

- upper limit of normal- 35 U/mL.
- In postmenopausal women :- lower cutoffs, 20 U/mL

- 85% of patients with epithelial ovarian cancer have >35 U/mL.
Diagnosis and Clinical Evaluation

- **Investigations**

**Tumor Markers**

- CA125 can be elevated:
  1. less frequently elevated in mucinous, clear cell, and borderline tumors compared to serous tumors.
  2. in other malignancies (pancreas, breast, colon, and lung cancer)
  3. in benign conditions and physiological states such as pregnancy, endometriosis, and menstruation.

*Many of these nonmalignant conditions are not found in postmenopausal women, improving the diagnostic accuracy of elevated CA125 in this population.*
Investigations

Tumor Markers:

- One of the limitations of CA125 is that 15% to 20% of ovarian cancers do not express the antigen.
- Though FDA approved, NCCN does not recommend use of biomarkers including CA-125 for estimating risk of cancer in case of pelvic mass.
- LDH (lactate dehydrogenase) — dysgerminoma
- HCG (human chorionic gonadotropin) — choriocarcinoma.
- AFP (alpha fetal protein) — endodermal sinus tumors
- Other routine tests (CBC, LFT, RFT, CXR)
Diagnosis and Clinical Evaluation

- **Investigations**, 

  - Initial imaging modality of choice
    - # for **benign vs malignant**

  - that US detects more stage I ovarian carcinomas than CA125 levels and physical examination
Diagnosis and Clinical Evaluation

- **Investigations**, benign:
  - smooth, thin walls; few, thin septations;
  - absence of solid components or mural nodularity.
Investigations,
mural nodules, mural thickening or irregularity, solid components, thick septations (3 mm) and associated findings such as ascites, peritoneal implants, and/or hydrenephrosis suggest malignancy.
Diagnosis and Clinical Evaluation

- Investigations

TVS is significantly more accurate
Investigations

Computed Tomography

- Not the study of choice to evaluate a suspected ovarian lesion.
- The sensitivity, specificity, and accuracy of CT for characterizing benign versus malignant lesions are reported to be 89%, 96% to 99%, and 92% to 94%, respectively.
### Diagnosis and Clinical Evaluation

- **Investigations**

**Computed Tomography**

- On CT, ovarian cancer demonstrates varied morphologic patterns, including a multilocular cyst with thick internal septations and solid mural or septal components, a partially cystic and solid mass, or a completely solid mass.
Diagnosis and Clinical Evaluation

- Investigations

Magnetic Resonance Imaging

- Complementary to US in the evaluation of a suspected ovarian lesion.
- As with CT, disease metastatic to the ovary is often indistinguishable from primary ovarian cancer on MRI scans.
- Both the colon and the stomach should be examined as potential primary tumor sites if an ovarian mass is detected.
Diagnosis and Clinical Evaluation

- Investigations

**Magnetic Resonance Imaging**

- Several studies have compared MRI to CT and US for characterizing adnexal masses, with mixed results.
- Both TVS and MRI have high sensitivity (97% and 100%, respectively) in the identification of solid components within an adnexal mass.
  - MRI, however, shows higher specificity (98% vs. 46%)
Investigations

Magnetic Resonance Imaging

- MRI was shown to be the most efficient second test when an indeterminate ovarian mass was detected at US.
- High cost of MRI precludes its use as a screening modality.
Investigations

**Positron Emission Tomography**
- little clinical role in the primary detection of a pelvic mass
- Appears to be promising for its potential to detect tumor prior to significant morphologic changes.
- US, CT, MRI, and FDG-PET all have a role to play in the accurate staging of ovarian cancer.
- These modalities also play a role in the monitoring of therapy and detection of recurrent disease.
Staging ...

- According to International Federation of Gynecology and Obstetrics (FIGO) Staging of Ovarian Neoplasms:

  - **Stage I. Growth limited to the ovaries**
    - Ia — one ovary involved
    - Ib — both ovaries involved
    - Ic — Ia or Ib and ovarian surface tumor, ruptured capsule, malignant ascites, or peritoneal cytology positive for malignant cells
Staging ...

Stage IC Cancer

- Bladder
- Fallopian tube
- Uterus
- Ovary
- Tumors spread to the ovarian surface
- Sigmoid colon

Malignant cells in a peritoneal washing
Stage II. Extension of the neoplasm from the ovary to the pelvis

IIa—extension to the uterus or fallopian tube

IIb—extension to other pelvic tissues

IIc—IIa or b and ovarian surface tumor, ruptured capsule, malignant ascites, or peritoneal cytology positive for malignant cells
Staging ...
Stage III. Disease extension to the abdominal cavity

IIIa—abdominal peritoneal surfaces with microscopic metastases

IIIb—tumor metastases < 2 cm in size

IIIc—tumor metastases > 2 cm in size or metastatic disease in the pelvic, paraaortic, or inguinal lymph nodes
Staging ...
- **Stage IV. Distant metastatic disease**

  - Malignant pleural effusion
  - Pulmonary parenchymal metastases
  - Liver or splenic parenchymal metastases (not surface implants)
  - Metastases to the supraclavicular lymph nodes or skin
Metastasis ...

- Typical spread—omentum, peritoneal surfaces such as undersurface of diaphragm, paracolic gutters and bowel serosa
- Lymphatics—follows bld supply thru infundibulopelvic lig to nodes in para aortic region
- Drainage thru broad lig and parametrium—involves ext iliac, obturator and hypogastric regions
- Along round lig—involves inguinal nodes
- Extra abd mets—pleura, liver, spleen, lung, bone and CNS
5-year survival rates for
- stage I and stage II ovarian cancer are 80% to 90% and 70%, respectively;
- for stages III and IV ranges from 5% to 30%.

Only 25% diagnosed in Stage I

In 1994, a NIH recommended that screening be offered to women with ≥ 2 first-degree relatives with ovarian carcinoma.

In practice, many women with a single first-degree relative are enrolled in screening programs
Unfortunately, there are no good screening methods for ovarian cancer at present; most use a combination of physical exam, CA125 levels, and TVS.

- No role of routine screening in general population.
- Some follow women with high risk factors (e.g., family history, BRCA mutation) using CA-125 and TVS.
Screening …

- Risk of Malignancy Index (RMI)

Most valuable clinical tool by combining serum CA125 values with ultrasound findings and menopausal status to calculate a Risk of Malignancy Index (RMI).

\[ \text{RMI} = U \times M \times \text{CA125} \]

1. ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions.

2. menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal

3. Serum CA125 in IU/ml and can vary between 0 and hundreds or even thousands of units.
Management ...

- Complete surgical staging
- Optimal reductive surgery
- Chemotherapy
- Clinical Trials
Management ...

- The treatment of ovarian cancer is based on the stage of the disease which is a reflection of the extent or spread of the cancer to other parts of the body.
- There are basically three forms of treatment of ovarian cancer:-
  1. The primary one is surgery at which time the cancer is removed from the ovary and from as many other sites as is possible
  2. Chemotherapy is the second important modality.
  3. Radiation treatment, which is used in only certain instances. It utilizes high energy x-rays to kill cancer cells.
Management ...

- Surgery
  - Surgery is the mainstay of both the diagnosis and the treatment of ovarian cancer.
  - A vertical incision is required for an adequate exploration of the upper abdomen.
  - The pelvis and upper abdomen are explored carefully to identify metastatic disease.
  - This is usually possible in the majority of stage I and stage II, but impossible in advanced cases.
Management …

- Surgery
  I. Complete hysterectomy & removal of tubes and ovaries
  II. • Lymph node evaluation
  III. • Omentectomy
  IV. • Intestinal resection
  V. • Peritoneal stripping/Tumor debulking
  VI. • Conservative management for those desiring to preserve fertility with early stage disease
Management ...

- **Surgery**

  1. In a young, nulliparous woman with unilateral tumour and no ascites (stage Ia), unilateral salpingo-oophorectomy may be done after careful exploration to exclude metastatic disease, and curettage of the uterine cavity to exclude a synchronous endometrial tumour.

- If the is subsequently found to be poorly differentiated or if the washings are positive, a second operation to clear the pelvis will be necessary.

- For older women who complete her family a total hysterectomy and bilateral salpingo-oophorectomy is usually done.
Management ...

- **Chemotherapy**
  - Women with stage Ia or Ib and well or moderately differentiated tumours will not require further treatment.
  - All other patient with invasive ovarian carcinoma require chemotherapy (stage II-IV – possibly stage Ic).
  - Drugs used are Carboplatin, cisplatin and taxol.
Radiation Therapy

- Currently, radiation therapy plays a limited role in the treatment of patients with epithelial ovarian cancer mainly because of radiation damage to the small bowel, liver, and kidneys.
- Radiation therapy has been used successfully in the treatment of patients with dysgerminoma.
Alternative Therapies

A number of alternative therapies have been applied for the treatment of epithelial ovarian cancer.

- **Cytokines** like interleukin-2 and interferon either alone or in combination with chemotherapy have shown some promising effects.

- **Monoclonal antibodies** directed against ovarian cancer-associated antigens, including CA-125, HMFG (human milk-fat globulin)
Management ...

Alternative Therapies

- **Recently,** antibodies against vascular epithelial growth factor (VEGF) have shown efficacy in patients with ovarian cancer. Anti-VEGF antibodies are currently being tested in combination with carboplatin and paclitaxel in first-line chemotherapy for ovarian cancer patients.

- **Gene therapy** trials have used different antitumor approaches, including the delivery of tumor suppressor gene p53 via recombinant adenovirus into the peritoneal cavities.
  - The early trials have not shown significant clinical response, mainly as a result of the inefficiency of intraperitoneal and intratumoral gene transfer.
Prognosis …

The prognosis for patients with ovarian cancer is primarily related to the stage of disease.

- **germ cell tumors** are associated with better 5-year survival rates than epithelial ovarian neoplasms.
- Patients with **dysgerminoma** have a 5-year survival rate of 95%.
- **Immature teratomas** are associated with 5-year survival rates of 70–80%.
- **endodermal sinus tumor** is associated with a 5-year survival rate of 60–70%.
Prognosis …
- Embryonal carcinoma, choriocarcinoma, and polyembryoma are very rare lesions, and it is difficult to assess 5-year survival estimates.
- Epithelial ovarian neoplasms of low malignancy potential are characterized by 5-year survival rates of 95%.
Five years survival rates

- Dysgerminoma
- Immature teratomas
- Endodermal sinus tumor
- Epithelial ovarian neoplasms
thank you