

Types of Ovarian Cancer: Germ Cell Tumor (GCT), Dysgerminoma, Metastatic Ovarian Cancer and more

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Ovarian cancer is becoming challenging every year due to the ever increasing number of new diagnoses. It is considered the 5th leading cause of cancer deaths among women; with about 14,000 deaths and more than 20,000 new cases every year.



Types of Ovarian Cancer

For a better understanding of ovarian tumors, microscopic anatomy of the ovary is mandatory. The ovary is composed of the three main entities that are made up of varying cells which give rise to the various types of tumors.

- **The cortex** contains both follicles and stroma. The follicles contain oocytes, which originate from germ cells and are responsible for the formation of germ cell tumors. The oocyte is surrounded by two layers of different cells called granulosa cells.

- **The mesenchyme from** the gonadal stroma which is composed of loose connective tissues filled with [blood vessels](#) and nerves. Tumors from these cells are known as stromal tumors.
- **The epithelial cubical cell layer** from the coelomic epithelium that surrounds the ovary and gives rise to the epithelial ovarian tumors.

Ovarian tumors can originate from different ovarian cell populations that have different pathological characteristics.

Epithelial tumors

These tumors arise from the **surface epithelium** of the ovary and constitute 60-70% of all ovarian tumors. They can differentiate into serous, mucinous, Brenner, endometrioid, small cell, clear cell and undifferentiated tumors. They can be benign, borderline, or malignant depending on the **stromal invasion**.

Serous tumors

These tumors are mostly **benign** rather than malignant i.e they have a 40% chance of malignancy.

The tumors are bilateral in 40% of cases and represent 40% of all ovarian tumors. They are common in young adults aged 30-40 years.

Serous cystadenocarcinoma are the malignant differentiation of serous tumors and are the most common types of malignant ovarian tumors. Serous tumors are composed mainly of **cysts with serous fluid** lined with **columnar ciliated epithelium** that may have a solid area that has **papillae**.

Malignant differentiation correlates with the solid areas within the tumors as well as the amount of **necrosis**. Borderline tumors have atypical cells but without invasion of the surrounding stroma. Malignant cystadenocarcinoma is characterized by **psammoma bodies**, which are calcified bodies within the papillae.

Mucinous tumors

Mucinous tumors are usually **unilateral** and can reach **huge sizes**. The cyst is lined with a single layer of **mucin-producing columnar cells** without cilia and sometimes **septa** originate within the cyst.

They can be classified as either benign, borderline or malignant. **Malignant mucinous tumors** (mucinous cystadenocarcinoma) carry a bad prognosis and can result in **pseudomyxoma peritonei** where the whole abdomen and pelvis is filled with mucinous cysts like [metastases](#), **mucinous ascites** and **fibrosis**.

Brenner tumors

They are also known as transitional tumors. They represent 1-2% of all ovarian tumors and only 8-10% are bilateral. They are more common among older women aged more than 40 years.

These can be solid or cystic. The tumor is mainly composed of nests or cysts of cells that resemble the **transitional epithelium of the urinary tract** and **spindle stromal cells** in-between. The cells are clear and have no mitotic figures, **pleomorphism** or

hyperchromasia.

Endometrioid carcinoma

They are rare tumors representing less than 5% of all ovarian tumors. Endometrioid carcinoma are usually malignant and commonly bilateral. The tumor resembles **endometrial carcinoma of the uterus** and may be simultaneously present. Microscopically, it consists of **glands of atypical cells** with large clear nuclei and prominent nucleoli.

Clear cell carcinoma

They are also known as mesonephroid tumors. Malignant clear cell carcinomas carry a **bad prognosis**. Cells are clear with prominent nucleus and glycogen-rich clear cytoplasm and contain abundant glycogen commonly known as hobnail cells. The cells can form **tubules** or **nests** that arrange in solid or cystic areas.

Sex cord tumors

Ovarian sex cord tumors arise from **stromal/sex cord granulosa cells, thecal cells** and **fibrocytes**. These cells are known for their hormonal function which may lead to **virilization** or **feminization** of the opposite sex. **CD56** has been proposed to identify sex cord tumors and to follow response to treatment as a marker.

Thecoma

This is almost always benign and unilateral. It is mostly considered to arise from hyperplasia of the cortical stroma and not a true neoplasm. It accounts for only 2% of ovarian tumors. The tumor originates from **theca follicular cells** and secretes **estrogen**. The presentation is usually post-menopausal bleeding in elderly women.

Granulosa cell tumor

This is malignant in one in every five patients. The tumor secretes **estrogen** responsible for **abnormal uterine bleeding**.

Fibroma

These are firm white grey tumors of **fibrocytes** which produce **concentric layers of collagen**. Unlike fibromas, they produce no hormones and they are more common among premenopausal women. The tumor is common in middle-aged females and is usually benign. It can be associated with **ascites** and **right side pleural effusion** to form what is called Meigs' syndrome.

Meigs' syndrome is the triad of right pleural effusion, ascites and **abdominal mass** mostly in ovarian sex cord/stromal tumor. It is most commonly found in fibroma but can also occur in granulosa cell tumors and sometimes even in Brenner's tumor. The effusion and ascites are reversible after removal of the tumor.

Tumors of testicular origin and can also be present in the ovary e.g. **Sertolli-Leydig cell tumor** and **Sertolli cell tumor**.

Gynandroblastoma

This is a rare tumor originating from both testicular and ovarian sex cord cells.

Germ cell tumor

Germ cell tumors include tumors which arise from the **ovum** and its precursor **germ cells**. Germ cell tumors can arise from the ovary or from other locations of the body due to germ cell migration. They represent 40-50% of all benign ovarian neoplasms. They are asymptomatic until complications such as torsion or rupture arise. Germ cell tumors include:

Germinomatous: germinoma/dysgerminoma of the ovary is composed of uniform cells that have clear cytoplasm and lymphocyte infiltration. The tumor is malignant and hCG is used as a marker in a small percentage of cases.

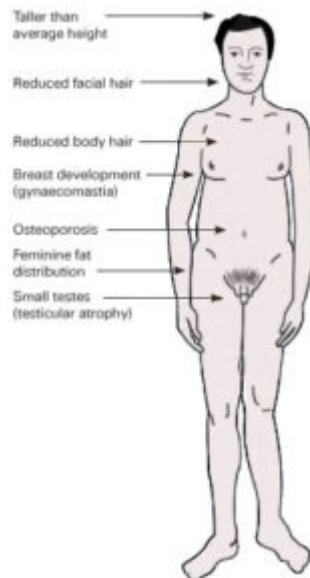


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Non-germinomatous include:

- **Teratoma:** tumor cells differentiate into derivatives of embryonic germ layers - ectoderm, mesoderm and endoderm. The tumors usually contain hair, teeth, eyes, limbs or bones tissues. It can be cystic or solid, benign or malignant. A mature cystic teratoma with a high grade of differentiation into mesodermal or ectodermal origin is known as a **dermoid cyst** and is usually benign.
- **Immature teratoma:** malignant germ cell tumor. The cells are poorly differentiated from any of the germ cell layer derivatives. Usually, it is common in young girls and has a good prognosis and responds well to therapy.
- **Dermoid cyst:** cystic teratoma that arises from embryonic totipotent germ cells and contains different developmental tissue origins and usually includes skin, teeth, hair, nails, thyroid tissue, eyes and bones or cartilage. It is a

benign tumor but close observation is required to avoid malignant transformation.

- **Choriocarcinoma:** germ cell tumor where the cells differentiate into placental trophoblasts and secrete beta-hCG without formation of placental villi. The tumor is malignant with early hematogenous spread to the [lung](#).
- **Embryonal carcinoma:** malignant tumor formed of sheets of poorly differentiated cells that secrete hCG and alpha-fetoprotein.
- **Yolk sac tumor/endometrial sinus tumor:** malignant tumor which secretes alpha-fetoprotein.
- **Polyembryoma:** rare malignant tumor that has been associated with **Klinefelter syndrome** (see picture beside).
- **Gonadoblastoma:** rare tumor composed of a mixture of cells including germ cells, Sertoli cells, stromal cells and granulosa cells. It is commonly associated with **genetic disorders** e.g. y chromosome and androgen insensitivity syndrome.

Risk Factors for Ovarian Cancer

There are several factors affecting the chances of ovarian cancer development. Several theories explain etiology of ovarian cancer:

- Incessant ovulation theory where increased activation of the ovary to form mature ova leads to haphazard multiplication and hence malignant conversion of the cells to form malignancy.
- The gonadotropin theory postulates that increase in the amount of gonadotropins lead to uncontrolled activation of the ovary and thus malignant conversion of the cells.
- Genetic theory where patients with a family history of associated conditions such as hereditary non-polyposis coli and BRCA-1/2 mutations are at an increased risk of developing ovarian cancer.

Therefore, most of the risk factors are related to genetic influence, **ovulation, or gonadotropin increase**. The lesser the ovulation and gonadotropin amount, the lower the risk of ovarian cancer occurring.

Pregnancy

Full-term pregnancies lower the risk of ovarian cancers with lower risk with each full-term pregnancy. The risk is higher in women who had late pregnancy or those who have never been pregnant. **Pregnancy hormones** prevent ovulation and lower the risk of ovarian cancer.

Contraception

Birth control with OCPs or injectable hormones lowers the risk of ovarian cancer significantly. This can also be due to **decreased ovulatory cycles** and thus protecting the ovary. [Progesterone](#) has some protective function against ovarian cancer.

Breastfeeding

[Breast feeding](#) after delivery will prevent ovulation for a longer period and also protects against ovarian cancer.

Age

The risk of ovarian cancer is more common in older women over the age of 60, especially those who fit the above criteria. It is less common in young girls due to less ovarian trauma during ovulation compared to elder women.

Medications

Clomiphene, which is used to stimulate ovulation for [infertility](#) treatment is associated with higher rates of ovarian cancer. **Estrogen** is associated with more risk of ovarian cancer after **menopause**, while **progesterone** is associated with less risk. **Androgens** are also associated with increased risk.

Genetic mutation

Having a first degree relative – mother, daughter or sister – with ovarian cancer carries a higher risk for developing ovarian cancer with the risk increasing with the number of relatives affected.

Other types of cancers known to be associated with an increased risk of developing ovarian cancer include [colorectal cancer](#) and [breast cancer](#). Mutations of PTEN, BRACA1, and BRACA2 genes are associated with a high risk of developing ovarian, breast, thyroid and pancreatic cancer.

Hereditary non-polyposis colon cancer (Lynch syndrome)

This is a genetic mutation associated with higher risk of colon cancer, ovarian cancer, and endometrial cancer.

Obesity and diet

Low fat and high fiber diets are associated with a decreased risk of developing ovarian cancer. Higher BMI is associated with a higher risk of developing ovarian cancer.

Talcum powder in women who have used it over their genital area has been associated with ovarian cancer. This can be explained by the fact that there may be contamination with **asbestos**.

Clinical Picture of Ovarian Cancer

General symptoms of malignancy may exist according to the cancer stage.

- Fever
- Loss of appetite
- Weight loss
- Bloating
- Mass effect on the bladder including frequent micturition and urgency
- Pelvic pain or dyspareunia.

Some patients will present with [metastases](#). Symptoms will vary depending on the location, including **ascites**, **pleural effusion** or **pelvic mass**.

Sister Mary Joseph sign is a nodule found in the **umbilicus** due to metastasis. Some ovarian cancers secrete hormones leading to a variety of symptoms:

- Amenorrhea
- Hirsutism
- Precocious puberty
- Postmenopausal bleeding
- Irregular uterine bleeding.

Emergent complications due to ovarian cysts include **rupture** and **torsion**. **Intestinal obstruction** is the most common cause of death.

Staging of Ovarian Cancer

FIGO classification of ovarian cancer is widely used for cancer staging as follows:

T: primary tumor stages

- **TX:** where the tumor can't be assessed

T1: tumor is limited to the ovaries

- **T1A:** tumor limited to one ovary and the capsule is intact with no peritoneal washings or malignant ascites
- **T1B:** tumor limited to both ovaries but the capsule is intact with no peritoneal seeding
- **T1C:** tumor limited to one or both ovaries but with capsule ruptured, peritoneal washings or malignant ascites

T2: tumor has extended to the pelvis

- **T2A:** tumor extended to the uterus or tubes but negative malignant ascites or peritoneal washings
- **T2B:** tumor extended to other pelvic tissues with negative malignant ascites or peritoneal washings
- **T2C:** tumor extended to the pelvis with positive malignant cells in ascites or peritoneal washings

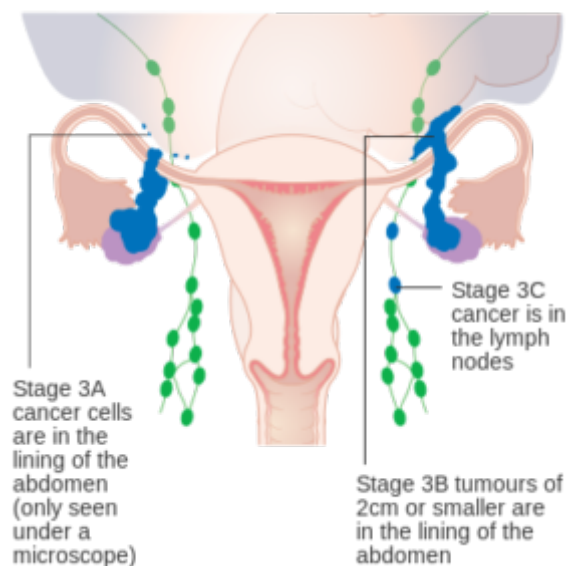


Image: "Diagram showing stage 3A to 3C ovarian cancer." by Cancer Research UK - Original email from CRUK. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

T3: tumor has extended outside the pelvis

- **T3A:** microscopic extension outside the pelvis with no macroscopic extension
- **T3B:** macroscopic extension outside the pelvis is less than 2 cm in greatest dimensions
- **T3C:** macroscopic metastases outside the pelvis more than 2 cm in greatest dimensions and/or positive regional lymph nodes
 - **N:** regional lymph nodes
 - **NX:** regional lymph nodes cannot be assessed
 - **NO:** no regional lymph node metastases
 - **N1:** positive regional lymph node metastases
 - **M:** distant metastases
 - **M0:** no distant metastases
 - **M1:** distant metastasis.

Diagnosis of Ovarian Cancer

There is no sensitive or specific screening method for early detection of ovarian cancer. **Transvaginal ultrasound** or **CA-125** are sometimes used.

CA-125

This is a **tumor marker** found in the blood of women with ovarian cancer, especially in elderly women. CA-125 is non-specific as it is elevated by many conditions other than ovarian cancer including menstruation, fibroids and **endometrial cancer**. It is considered for screening in women with high risk e.g. **BRACA1 & BRACA2 mutations**.

Tumor markers are generally used to monitor response to treatment and possible recurrence.

Ovarian tumor markers

They are non-specific markers and can be elevated by other conditions. **Clinical correlation** and **imaging studies** are mandatory before treatment with **chemotherapy** or **surgery**.

- **CA-125:** usually elevated in epithelial ovarian tumors
- **Alpha-fetoprotein, hCG:** both usually elevated in germ cell tumors
- **LDH lactate dehydrogenase:** elevated with dysgerminoma
- **Hormonal markers** e.g. **estrogen**, **testosterone** and **inhibin:** elevated in stromal tumors.

Trans-vaginal and trans-abdominal ultrasound

These can be used with CA-125 for screening or sometimes help with staging.

CT scan & MRI

Both are used for better staging of the disease' extent in the pelvis.

Treatment of Ovarian Cancer

Stage 1A, where the cancer is limited to one ovary, is treated by **unilateral**

oophorectomy, especially in young women who want to conceive.

Stage IV is treated with **chemotherapy** only. Some cases will benefit from **neoadjuvant chemotherapy** to become operable.

For operable cases, **radical hysterectomy** involving **removal of the uterus, fallopian tubes, ovaries and momentum** is carried out. Surgery will provide a **biopsy** for diagnosis, better staging and debulking or excision of the tumor.

Surgery can also extend to **lymphadenectomy, splenectomy, appendectomy, diaphragmatic resection, intestinal resection**, and **pelvic exenteration** depending on the extent of the disease.

Chemotherapy

Adjuvant chemotherapy is given after surgery for high-grade tumors while neo-adjuvant chemotherapy can be given prior to surgery to improve outcome and help with tumor resection. Chemotherapy regimens are based on **carboplatin** and **paclitaxel**.

Bilateral oophorectomy in young women necessitates **hormonal therapy** with estrogen to avoid early menopausal symptoms including **hot flashes, cardiovascular disorders**, and **osteoporosis**.

Radiation therapy can be used in advanced cases for **palliation** with chemotherapy or after surgery, especially for **radiosensitive dysgerminoma**.

References

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