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# **About Ovarian Cancer**

#### **Overview and Types**

If you have been diagnosed with ovarian cancer or are worried about it, you likely have a lot of questions. Learning some basics is a good place to start.

What Is Ovarian Cancer?

#### **Research and Statistics**

See the latest estimates for new cases of ovarian cancer and deaths in the US and what research is currently being done.

- Key Statistics for Ovarian Cancer
- What's New in Ovarian Cancer Research?

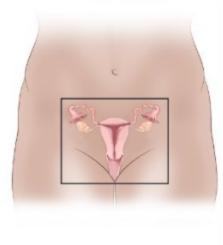
# What Is Ovarian Cancer?

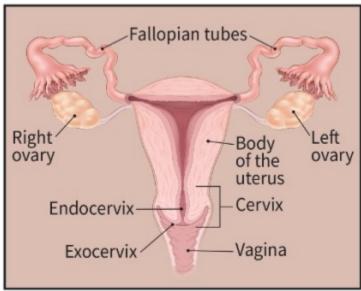
Cancer starts when cells in the body begin to grow out of control. Cells in nearly any part of the body can become cancer and can spread. To learn more about how cancers start and spread, see What Is Cancer?<sup>1</sup>

Ovarian cancers were previously believed to begin only in the ovaries, but recent evidence suggests that many ovarian cancers may actually start in the cells in the far (distal) end of the fallopian tubes.

#### What are the ovaries?

Ovaries are reproductive glands found only in females (women). The ovaries produce eggs (ova) for reproduction. The eggs travel from the ovaries through the fallopian tubes into the uterus where the fertilized egg settles in and develops into a fetus. The ovaries are also the main source of the female hormones estrogen and progesterone. One ovary is on each side of the uterus.





The ovaries are mainly made up of 3 kinds of cells. Each type of cell can develop into a different type of tumor:

- Epithelial tumors start from the cells that cover the outer surface of the ovary. Most ovarian tumors are epithelial cell tumors.
- Germ cell tumors start from the cells that produce the eggs (ova).
- Stromal tumors start from structural tissue cells that hold the ovary together and produce the female hormones estrogen and progesterone.

Some of these tumors are benign (non-cancerous) and never spread beyond the ovary. Malignant (cancerous) or borderline (low malignant potential) ovarian tumors can spread (metastasize) to other parts of the body and can be fatal.

# **Epithelial ovarian tumors**

Epithelial ovarian tumors start in the outer surface of the ovaries. These tumors can be benign (not cancer), borderline (low malignant potential), or malignant (cancer).

#### Benign epithelial ovarian tumors

Epithelial ovarian tumors that are benign don't spread and usually don't lead to serious illness. There are several types of benign epithelial tumors including serous cystadenomas, mucinous cystadenomas, and Brenner tumors.

#### **Borderline Epithelial Tumors**

When looked at in the lab, some ovarian epithelial tumors don't clearly appear to be cancerous and are known as *borderline epithelial ovarian cancer*. The two most common types are atypical proliferative serous carcinoma and atypical proliferative mucinous carcinoma. These tumors were previously called tumors of *low malignant potential (LMP tumors)*. These are different from typical ovarian cancers because they don't grow into the supporting tissue of the ovary (called the ovarian *stroma*). If they do spread outside the ovary, for example, into the abdominal cavity (belly), they might grow on the lining of the abdomen but not into it.

Borderline tumors tend to affect younger women than the typical ovarian cancers. These tumors grow slowly and are less life-threatening than most ovarian cancers.

#### Malignant epithelial ovarian tumors

Cancerous epithelial tumors are called *carcinomas*. About 85% to 90% of malignant ovarian cancers are epithelial ovarian carcinomas. These tumor cells have several features (when looked at in the lab) that can be used to classify epithelial ovarian carcinomas into different types. The *serous* type is by far the most common, and can include high grade and low grade tumors. The other main types include *mucinous*, *endometrioid*, and *clear cell*.

- Serous carcinomas (52%)
- Clear cell carcinoma (6%)
- Mucinous carcinoma (6%)
- Endometrioid carcinoma (10%)

Each ovarian cancer is given a grade, based on how much the tumor cells look like normal tissue:

- Grade 1 epithelial ovarian carcinomas look more like normal tissue and tend to have a better prognosis (outlook).
- Grade 3 epithelial ovarian carcinomas look less like normal tissue and usually have

a worse outlook.

Other traits are also taken into account, such as how fast the cancer cells grow and how well they respond to chemotherapy, to come up with the tumor's *type:* 

- Type I tumors tend to grow slowly and cause fewer symptoms. These tumors also seem not to respond well to chemotherapy. Low grade (grade 1) serous carcinoma, clear cell carcinoma, mucinous carcinoma and endometrioid carcinoma are examples of type I tumors.
- Type II tumors grow fast and tend to spread sooner. These tumors tend to respond better to chemotherapy. High grade (grade 3) serous carcinoma is an example of a type II tumor.

#### Other cancers that are similar to epithelial ovarian cancer

#### Primary peritoneal carcinoma

Primary peritoneal carcinoma (PPC) is a rare cancer closely related to epithelial ovarian cancer. At surgery, it looks the same as an epithelial ovarian cancer that has spread through the abdomen. In the lab, PPC also looks just like epithelial ovarian cancer. Other names for this cancer include *extra-ovarian* (meaning outside the ovary) *primary peritoneal carcinoma* (EOPPC) and *serous surface papillary carcinoma*.

PPC appears to start in the cells lining the inside of the fallopian tubes.

Like ovarian cancer, PPC tends to spread along the surfaces of the pelvis and abdomen, so it is often difficult to tell exactly where the cancer first started. This type of cancer can occur in women who still have their ovaries, but it is of more concern for women who have had their ovaries removed to prevent ovarian cancer. This cancer does rarely occur in men.

Symptoms of PPC are similar to those of ovarian cancer, including abdominal pain or bloating, nausea, vomiting, indigestion, and a change in bowel habits. Also, like ovarian cancer, PPC may elevate the blood level of a tumor marker called CA-125.

Women with PPC usually get the same treatment as those with widespread ovarian cancer. This could include surgery to remove as much of the cancer as possible (a process called debulking that is discussed in the section about <a href="surgery">surgery</a><sup>2</sup>), followed by <a href="mailto:chemotherapy">chemotherapy</a> like that given for ovarian cancer. Its outlook is likely to be similar to

widespread ovarian cancer.

#### Fallopian tube cancer

This is another rare cancer that is similar to epithelial ovarian cancer. It begins in the tube that carries an egg from the ovary to the uterus (the fallopian tube). Like PPC, fallopian tube cancer and ovarian cancer have similar symptoms. The treatment for fallopian tube cancer is much like that for ovarian cancer, but the outlook (prognosis) is slightly better.

## **Ovarian germ cell tumors**

Germ cells usually form the ova or eggs in females and the sperm in males. Most ovarian germ cell tumors are benign, but some are cancerous and may be life threatening. Less than 2% of ovarian cancers are germ cell tumors. Overall, they have a good outlook, with more than 9 out of 10 patients surviving at least 5 years after diagnosis. There are several subtypes of germ cell tumors. The most common germ cell tumors are *teratomas*, *dysgerminomas*, *endodermal sinus tumors*, and *choriocarcinomas*. Germ cell tumors can also be a mix of more than a single subtype.

#### **Teratoma**

Teratomas are germ cell tumors with areas that, when seen under the microscope, look like each of the 3 layers of a developing embryo: the *endoderm* (innermost layer), *mesoderm* (middle layer), and *ectoderm* (outer layer). This germ cell tumor has a benign form called *mature* teratoma and a cancerous form called *immature* teratoma.

The mature teratoma is by far the most common ovarian germ cell tumor. It is a benign tumor that usually affects women of reproductive age (teens through forties). It is often called a *dermoid cyst* because its lining is made up of tissue similar to skin (dermis). These tumors or cysts can contain different kinds of benign tissues including, bone, hair, and teeth. The patient is cured by surgical removal of the cyst, but sometimes a new cyst develops later in the other ovary.

Immature teratomas are a type of cancer. They occur in girls and young women, usually younger than 18. These are rare cancers that contain cells that look like those from embryonic or fetal tissues such as connective tissue, respiratory passages, and brain. Tumors that are relatively more mature (called *grade 1 immature teratoma*) and haven't spread beyond the ovary are treated by surgical removal of the ovary. When they have spread beyond the ovary and/or much of the tumor has a very immature appearance (grade 2 or 3 immature teratomas), chemotherapy is recommended in addition to

surgery.

#### **Dysgerminoma**

This type of cancer is rare, but it is the most common ovarian germ cell cancer. It usually affects women in their teens and twenties. Dysgerminomas are considered malignant (cancerous), but most don't grow or spread very rapidly. When they are limited to the ovary, more than 75% of patients are cured by surgically removing the ovary, without any further treatment. Even when the tumor has spread further (or if it comes back later), surgery, radiation therapy, and/or chemotherapy are effective in controlling or curing the disease in about 90% of patients.

#### Endodermal sinus tumor (yolk sac tumor) and choriocarcinoma

These very rare tumors typically affect girls and young women. They tend to grow and spread rapidly but are usually very sensitive to chemotherapy. Choriocarcinoma that starts in the placenta (during pregnancy) is more common than the kind that starts in the ovary. Placental choriocarcinomas usually respond better to chemotherapy than ovarian choriocarcinomas do.

#### **Ovarian stromal tumors**

About 1% of ovarian cancers are ovarian stromal cell tumors. More than half of stromal tumors are found in women older than 50, but about 5% of stromal tumors occur in young girls.

The most common symptom of these tumors is abnormal vaginal bleeding. This happens because many of these tumors produce female hormones (estrogen). These hormones can cause vaginal bleeding (like a period) to start again after menopause. In young girls, these tumors can also cause menstrual periods and breast development to occur before puberty.

Less often, stromal tumors make male hormones (like testosterone). If male hormones are produced, the tumors can cause normal menstrual periods to stop. They can also make facial and body hair grow. If the stromal tumor starts to bleed, it can cause sudden, severe abdominal pain.

Types of malignant (cancerous) stromal tumors include *granulosa cell* tumors (the most common type), *granulosa-theca* tumors, and *Sertoli-Leydig cell* tumors, which are usually considered low-grade cancers. *Thecomas* and *fibromas* are benign stromal tumors. Cancerous stromal tumors are often found at an early stage and have a good

outlook, with more than 75% of patients surviving long-term.

# **Ovarian cysts**

An ovarian cyst is a collection of fluid inside an ovary. Most ovarian cysts occur as a normal part of the process of ovulation (egg release) -- these are called *functional cysts*. These cysts usually go away within a few months without any treatment. If you develop a cyst, your doctor may want to check it again after your next menstrual cycle (period) to see if it has gotten smaller.

An ovarian cyst can be more concerning in a female who isn't ovulating (like a woman after menopause or a girl who hasn't started her periods), and the doctor may want to do more tests. The doctor may also order other tests if the cyst is large or if it does not go away in a few months. Even though most of these cysts are benign (not cancer), a small number of them could be cancer. Sometimes the only way to know for sure if the cyst is cancer is to take it out with surgery. Cysts that appear to be benign (based on how they look on <u>imaging tests</u><sup>4</sup>) can be observed (with repeated physical exams and imaging tests), or removed with surgery.

## **Hyperlinks**

- 1. www.cancer.org/cancer/cancer-basics/what-is-cancer.html
- 2. www.cancer.org/cancer/ovarian-cancer/treating/surgery.html
- 3. www.cancer.org/cancer/ovarian-cancer/treating/chemotherapy.html
- 4. www.cancer.org/treatment/understanding-your-diagnosis/tests/imaging-radiology-tests-for-cancer.html

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# **Key Statistics for Ovarian Cancer**

The American Cancer Society estimates for ovarian cancer in the United States for

#### 2019 are:

- About 22,530 women will receive a new diagnosis of ovarian cancer.
- About 13.980 women will die from ovarian cancer.

Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 78. Her lifetime chance of dying from ovarian cancer is about 1 in 108. (These statistics don't count low malignant potential ovarian tumors.)

This cancer mainly develops in older women. About half of the women who are diagnosed with ovarian cancer are 63 years or older. It is more common in white women than African-American women.

The rate at which women are diagnosed with ovarian cancer has been slowly falling over the past 20 years.

Visit the American Cancer Society's Cancer Statistics Center<sup>1</sup> for more key statistics.

## **Hyperlinks**

- 1. https://cancerstatisticscenter.cancer.org/
- 2. https://seer.cancer.gov/csr/1975\_2014/

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# What's New in Ovarian Cancer Research?

#### Risk factors and causes

Scientists continue to study the genes responsible for familial ovarian cancer. This research is beginning to yield clues about how these genes normally work and how disrupting their action can lead to cancer. This information eventually is expected to lead to new drugs for preventing and treating familial ovarian cancer.

Research in this area has already led to better ways to detect high-risk genes and assess a woman's ovarian cancer risk. A better understanding of how genetic and hormonal factors (such as oral contraceptive use) interact may also lead to better ways to prevent ovarian cancer.

#### Prevention

New information about how much *BRCA1* and *BRCA2* gene mutations increase ovarian cancer risk is helping women make practical decisions about prevention. For example, mathematical models have been developed that help estimate how many years of life an average woman with a *BRCA* mutation might gain by having both ovaries and fallopian tubes removed to prevent a cancer from developing. Studies have shown that fallopian tube cancers develop in women with *BRCA* gene mutations more often than doctors had previously suspected. However, it is important to remember that although doctors can predict the average outcome of a group of many women, it is still impossible to accurately predict the outcome for any individual woman.

Studies suggest that many primary peritoneal cancers and some ovarian cancers (such as high-grade serous carcinomas) actually start in the fallopian tubes. According to this theory, the early changes of these cancers can start in the fallopian tubes. Cells from these very early fallopian tube cancers can become detached and then stick to the surface of the peritoneum or the ovaries. For reasons that are still not understood, these cancer cells may grow more rapidly in their new locations.

This theory has important implications for preventing ovarian cancer because having the ovaries removed early can cause problems from lack of estrogen, such as bone loss, cardiovascular disease, and menopause symptoms. Some experts have suggested recently that some women who are concerned about their ovarian cancer risk (especially those with a strong family history and/or *BRCA* gene mutations) consider

having just their fallopian tubes removed first. They then can have their ovaries removed when they are older. This approach lets women keep their ovaries functioning for longer, but because of that, it might not help breast cancer risk as much. This is an active area of research.

Other studies are testing new drugs for ovarian cancer risk reduction.

Researchers are constantly looking for clues such as lifestyle, diet, and medicines that may alter the risk of ovarian cancer.

## **Early detection**

Being able to find ovarian cancer early could have a great impact on the cure rate. Researchers are testing new ways to screen women for ovarian cancer. One method being tested is looking at the pattern of proteins in the blood (called *proteomics*) to find ovarian cancer early.

## **Imaging**

The use of new imaging techniques such as Functional MRI are being evaluated in ovarian cancers. PET/CT scans are also being studied to see where they may be best used for ovarian cancer.

# **Diagnosis**

For women who have an ovarian tumor, a test called OVA1 can measure the levels of 5 proteins in the blood. The levels of these proteins, when looked at together, are used to determine whether a woman's tumor should be considered low risk or high risk. If the tumor is labeled "low risk" based on this test, the woman is not likely to have cancer. If the tumor is considered "high risk," the woman is more likely to have a cancer, and should see a specialist (a gynecologic oncologist). This test is NOT a screening test and it is NOT a test to decide if you should have surgery or not it is meant for women who have an ovarian tumor where surgery has been decided but have not yet been referred to a gynecologic oncologist.

#### **Treatment**

Treatment research includes testing the value of currently available methods as well as developing new approaches to treatment.

#### Chemotherapy

New chemotherapy (chemo) drugs and drug combinations are being tested.

When the drugs cisplatin and carboplatin stop working, the cancer is said to be *platinum resistant*. Studies are looking for many ways to make these cancers sensitive to these drugs again. Different strategies include:

- Looking closely at what specific mechanisms and proteins are involved in the making ovarian cancer cells resistant.
- Developing drugs that can keep the cancer cells from becoming resistant to the chemo by blocking channels that pump chemotherapy out of the cancer cell.
- Trying to determine the details of certain cancer cells where the DNA is not damaged by chemotherapy which allows it to keep growing.

Although carboplatin is preferred over cisplatin in treating ovarian cancer if the drug is to be given IV, cisplatin is used in intraperitoneal (IP) chemotherapy. Studies are looking at giving carboplatin for IP chemo.

Another approach is to give IP chemo during surgery using heated drugs. This, known as heated intraperitoneal chemotherapy or HIPEC, can be effective. More studies are showing this to be beneficial and may improve how long a woman lives.

#### **Targeted therapy**

Targeted therapy is a newer type of cancer treatment that uses drugs or other substances to identify and attack cancer cells while doing little damage to normal cells. Each type of targeted therapy works differently, but they all attack the cancer cells' inner workings the programming that makes them different from normal, healthy cells. Bevacizumab (Avastin) is the targeted therapy that has been studied best in ovarian cancer, but other similar drugs, like pembrolizumab, are being looked at, as well.

Catumaxomab is a drug being studied specifically for people with malignant ascites (fluid buildup in the abdomen [belly] caused by cancer cells). It works by targeting 3 different cell types including tumor cells and white blood cells called T-cells.

Poly(ADP-ribose) polymerases (PARPs) are enzymes that have been recently recognized as key regulators of cell survival and cell death. Drugs that inhibit PARP-1 (called PARP inhibitors) have been approved for patients with ovarian cancer caused by mutations in *BRCA1* and *BRCA2*. New evidence shows that ovarian cancers can also become resistant to treatment with PARP inhibitors. Research is trying to find ways to

counteract this process.

#### **Genetic therapies**

For ovarian and breast cancers that are caused by the BRCA 1 mutation, it has been shown that low levels of the BRCA 1 mutation are associated with good responses to PARP inhibitors and platinum drugs, like cisplatin and carboplatin. New research shows that microRNA, very small pieces of RNA (substances that carry genetic messages for DNA), can also lower levels of BRCA1 mutations. New drugs that can target these tiny pieces of RNA are being investigated as possible ways to treat these cancers.

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