CA 125 LEVELS
Your Guide

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Introduction

Women who are suspected of having or have been diagnosed with fallopian tube, ovarian, or primary peritoneal cancer often undergo a blood test to measure their serum CA 125 level.

The association between fallopian tube, ovarian, and primary peritoneal cancer and serum CA 125 levels can be confusing. There is frequent misunderstanding about the implication of serum CA 125 levels as they relate to the diagnosis and management of this group of closely related malignancies.

This booklet explains the basics of what patients need to know about CA 125 — what it is, what it’s measuring, and what the values mean. This information will help you better understand how this test is used and interpreted in your treatment and follow-up.
What is CA 125?

Cancer Antigen 125 (CA 125) is a substance found in the blood called a glycoprotein (a sugar-associated protein). It is commonly referred to as a “biomarker” — or “tumor marker” — because it may provide information about the biological state of a disease (ovarian, fallopian tube or primary peritoneal cancer), and is obtained by a blood sample from which a level can be measured.

CA 125 levels are commonly used to assist in diagnosing and assessing response to treatment for ovarian, fallopian tube, and primary peritoneal cancer. However, it is not a perfect test because it is only elevated in approximately 50% of women who have early-stage ovarian cancer and 85% of women with advanced ovarian cancer. In other words, CA 125 levels may not be elevated in someone with cancer. Additionally, it can be elevated in someone who does not have cancer, and the magnitude of the CA 125 level itself does not necessarily correlate with the extent of cancer in someone who actually has cancer with an elevated CA 125 level.

CA 125 levels are most useful when a patient with confirmed ovarian, fallopian tube, or primary peritoneal cancer has serial measurements that correlate with different points in their disease course. For example, following the trend in CA 125 levels before, during and after treatment can help identify responders and non-responders to therapy as well as give warnings about recurrence of disease.
The history of the CA 125 test

The current CA 125 blood test is the second generation of a test first introduced in the early 1980s as a possible treatment. Based on early experience with immune therapy for cancer, investigators started searching for something unique on the surfaces of ovarian cancer cells that could be used to trigger recognition of tumor cells by the immune system. After 125 attempts, an antibody was found that seemed to do the trick.

The antibody was termed OC-125 (for the 125th antibody tested against ovarian cancer cells) and recognized a tumor cell surface signal termed CA 125. Unfortunately, attempts to use this antibody in treatment were not successful. However, astute researchers recognized an interesting phenomenon about the protein and antibody they were testing — the levels in the blood seemed to correlate with the status of the ovarian cancer.

New studies were launched to see if CA 125 might be useful as a test to diagnose and follow ovarian cancer patients. Eventually, a CA 125 level of 35 units was found to be a useful cutoff point, with 99% of healthy women having values less than 35. Levels above 35 units are certainly seen in healthy women, but beyond the cutoff point of 35, the higher the value, the more likely there is trouble somewhere in the body. Women with ovarian cancer often have levels measured in hundreds and even thousands of units.

So, the CA 125 test is helpful, but not perfect. Individual values are hard to interpret, so many physicians focus on the trend in values over a course of time rather than on any individual value. Time trends help to put the individual values into perspective to get a “picture” of what might be going on in a particular situation.
CA 125 and false elevation

Normal tissues, including ovarian, pancreatic, and breast cells, and the lining tissue of the abdomen and chest all make and release low levels of CA 125. Since the CA 125 test reflects the amount of protein (often called antigen) released into the bloodstream from specific organs, conditions that cause irritation or inflammation can change the test result. Ovarian cancer not only increases the number of cells that make CA 125, but also perturbs or inflames the abdominal lining, which contains “normal” cells that make and release CA 125. So, it’s not surprising that CA 125 is elevated in ovarian cancer and in some other cancers in the abdomen.

But other, noncancerous conditions can elevate the CA 125 value, such as inflammatory conditions of the abdomen (diverticulitis, peritonitis, pelvic inflammatory disease, inflammatory bowel disease, tuberculosis, and pancreatitis), cardiac conditions such as congestive heart failure, liver disease, recent surgery, and benign gynecologic conditions such as fibroids, endometriosis, ectopic pregnancy, or a ruptured cyst. In some situations, CA 125 is even used to monitor the effects of treatment for benign conditions such as endometriosis. These other diagnoses must be considered in the interpretation of an elevated CA 125 value.
Potential applications of the CA 125 test

The CA 125 test is used in a variety of situations during the course of diagnosis, treatment, and follow-up of ovarian and other closely related cancers, such as primary peritoneal and fallopian tube cancers.

Five primary roles for CA 125 assessment have been established, with varying degrees of clinical use and reliability. The five major roles are:

**Outcome prediction:** CA 125 has been studied for its ability to predict treatment outcome in women with ovarian cancer and closely related cancers, such as fallopian tube and primary peritoneal cancer.

**Detection:** CA 125 is widely used to detect recurrent ovarian cancer in women who have been previously treated.

**Monitoring:** CA 125 is used throughout the course of chemotherapy or radiation to monitor or assess treatment effectiveness.

**Screening:** CA 125 is often used to screen for ovarian, primary peritoneal, and fallopian tube cancers in high-risk women or in women with abnormal findings on examination or ultrasound.

**Pelvic mass triage:** CA 125 is included as a marker to help determine the risk of a malignancy preoperatively.

### Outcome prediction

While more research is needed to completely determine how well changes in CA 125 levels can predict the success of cancer treatment, several recent studies have sought to answer the question, “If, during the first time a woman is treated for ovarian cancer, her CA 125 level returns to ‘normal,’ will she have a better chance of survival?”

The answer seems to be “yes,” but with a note of caution. This conclusion is a generality, applied to a study population when looking at the trends for large groups of women. Extrapolating this data about CA 125 levels may not be accurate for individual women.

### Recurrent disease detection

In a woman with confirmed ovarian, fallopian tube, or primary peritoneal cancer and an elevated CA 125 level that normalizes after treatment, a new rising CA 125 level during surveillance is a very reliable indicator of recurrent disease. In fact, CA 125 levels can be elevated before an exam and/or scan (CT or PET) to detect evidence of recurrent cancer. This is called a “biochemical recurrence.” The role of CA 125 level monitoring for recurrence and when to start treatment for recurrent disease should be discussed with your gynecologic oncologist.
While there are certainly exceptions, generally, an upward trend in CA 125 levels over a series of tests strongly suggest that a woman is experiencing a recurrence of her disease. Keep in mind that some women develop a recurrence without an associate rise in CA 125 level, and conversely some women have a modest rise in CA 125 levels but never develop recurrent disease.

Good evidence suggests that using CA 125 levels to determine a biochemical recurrence leading to early initiation of therapy for recurrent disease does not result in an overall improved survival compared to waiting to start recurrent disease therapy when clinical and radiographic findings confirm recurrence. Furthermore, following CA 125 values more closely causes physicians to administer more chemotherapy, thus worsening patient’s quality of life without improving outcomes.

The role of monitoring CA 125 levels for detecting recurrent disease should be discussed with your doctor.

**Treatment monitoring**

A downtrending CA 125 level along with radiographic imaging and physical exam are the best ways to confirm treatment effectiveness.

The usefulness of the CA 125 level depends on the starting value. Monitoring is most accurate when patients have an elevated initial CA 125 value. Some information is emerging suggesting that the trends in CA 125 values within what is generally considered the normal range may also provide clues to treatment success.

It is vital to stress that this test represents just a piece of the puzzle, and a number of other factors are considered in determining whether any given therapy is working to fight the cancer. It is also important to emphasize that CA 125 values may go up or down for a variety of reasons and, because of this, the test may not accurately reflect disease status. This is particularly true when the values are in the normal range or are only minimally elevated. Most clinicians rely on how the numbers change over time and not on one test result alone.
Monitoring changes in the CA 125 value while on treatment can provide some of the earliest clues that your therapy is working. However, it’s important not to overinterpret the values. For instance, some chemotherapy and biologic agents used in recurrent disease treatment, such as pegylated liposomal doxorubicin (Doxil) and topotecan (Hycamtin), require closer scrutiny as a significant number of patients may have a rise in their CA 125 values — as much as 30% — after their first cycle of chemotherapy, and yet go on to respond to these drugs upon continued administration. Some patients even have a rise in CA 125 after their second or third cycle and still had a favorable treatment outcome. Similarly, bevacizumab, a targeted biologic agent, may cause elevated CA 125 values despite having a positive treatment effect. So, CA 125 values can and do fluctuate. Major treatment decisions, such as changing or discontinuing treatment, depend on multiple factors that you and your physician will consider. The trend in your CA 125 values is only one of these factors.

Ovarian cancer screening
As is the case with most cancers, early detection of ovarian cancers leads to a higher cure rate. Because there is not yet a highly effective screening test for ovarian cancer, and the symptoms of this cancer are variable, many women are diagnosed at a later, less treatable stage. Therefore, much effort is directed toward being able to screen for this cancer, or at least detect it at its earliest and most treatable stage.

The CA 125 test alone has proven to be ineffective in screening for ovarian cancer in the general population. In fact, one recent study of women receiving an annual CA 125 and an ultrasound led to an increase in adverse outcomes compared to women who did not undergo screening because the abnormal test results led to unnecessary surgical procedures. As explained earlier, many factors influence “the number,” making it unreliable as a screening test for ovarian or any other reproductive cancer. The test misses up to 50% of early ovarian cancers, when treatment is most successful.
Furthermore, the test is falsely elevated in a portion of the population due to conditions unrelated to cancer. CA 125 is especially unreliable in screening premenopausal women because both ovulation and menstruation can cause elevated levels.

However, researchers continue to look into other possibilities for ovarian cancer screening. One option that seems to hold promise is the use of several tests, including the CA 125 test, performed in sequence or together as indicators of the presence of ovarian cancer. Some recent research has shown promise using the CA 125 test over time to look for changes within an individual patient followed by ultrasound in those with elevated values. But it is too early to know if this approach will prove beneficial for the general population in terms of cost and lives saved.

### Pelvic mass triage

CA 125 has been used as part of a panel of biomarkers to determine the likelihood that a mass on imaging or exam is malignant. CA 125 is one of several markers in multianalyte platforms. These tests estimate the risk of a malignancy preoperatively to allow proper triage of a patient to a gynecologic oncologist in the event of an elevated risk score.

### Recent FDA statement

In September 2016 the U.S. Food & Drug Administration (FDA) issued a safety communication that recommends against using tests that are currently marketed for ovarian cancer screening. According to the statement, “The Agency is especially concerned about delaying effective preventive treatments for women who show no symptoms, but who are still at increased risk for developing ovarian cancer. Based on currently available information, the FDA recommends against using currently offered tests to screen for ovarian cancer.”

The FDA made the following recommendations regarding ovarian cancer screening tests for women, including those at increased risk of developing ovarian cancer:

- Be aware that there is currently no safe and effective ovarian cancer screening test.
- Do not rely on ovarian cancer screening test results to make health or treatment decisions.
- Talk to your doctor about ways to reduce your risk of developing ovarian cancer, especially if you have a family history of ovarian cancer, or have the BRCA1 or BRCA2 genetic mutations.
Future interventions
Many novel applications for CA 125 are emerging including using this test to assess response to neoadjuvant chemotherapy and predict the ability of the surgeon to cytoreduce. Additionally, CA 125 can be used in dynamic modeling to assess the efficacy of drugs in early development.

A final note
We urge individuals diagnosed with ovarian cancer to keep in mind that the CA 125 test is only one indication of how well the treatment is working. Gynecologic oncologists, who are obstetrician-gynecologists with an additional three to four years of training in the comprehensive treatment of patients with gynecologic cancers, are specifically knowledgeable about how to interpret a CA 125 test result in the treatment of ovarian cancer.
How you can help

• Raise awareness about gyn cancers.
• Donate to the Foundation for Women’s Cancer online.
• Host your own fundraising event or partner with the Foundation.
• Give a Matching Gift through your employer to the Foundation.
• Give gifts of stock or securities to the Foundation.
• Designate a planned gift to the Foundation.

The Foundation for Women’s Cancer offers many resources for patients, advocates and the general public, including Survivor Courses around the U.S., webinars and an online education series. To make a gift or for additional information, please email the Foundation at Info@foundationforwomenscancer.org or call 312.578.1439.

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