



FOUNDATION FOR
WOMEN'S CANCER

 Gynecologic Cancer
Awareness • Research • Education

Understanding CA 125 Levels

A GUIDE FOR OVARIAN CANCER PATIENTS

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The Foundation for Women's Cancer was established by the Society of Gynecologic Oncology in 1991 to increase funding for research and training, and to develop educational and awareness programs for women. These programs focus on the prevention, early detection and optimal treatment of gynecologic cancers.

As a 501(c)(3) not-for-profit charitable organization, the Foundation for Women's Cancer raises funds to support these programs from both public and private sources.

INTRODUCTION

Women who are suspected of having ovarian cancer and women who have been diagnosed with ovarian cancer often receive a blood test to measure their CA 125 level.

This association between ovarian cancer and CA 125 often leads to confusion and misunderstanding about what this test means for diagnosis of ovarian cancer and/or its impact on the clinical management of ovarian cancer.

This booklet will take you through the basics of what you need to know about CA 125 — what it is, what it's measuring and what the values mean. And hopefully, this information will help you better understand how this test is used and interpreted in your treatment and follow-up.

The information in this booklet was originally provided to over 300 women who participated in a free telephone workshop organized by the Foundation for Women's Cancer. Dr. Thomas J. Herzog, Paul & Carolyn Flory Professor in OB/GYN Clinical Director, University of Cincinnati Cancer Institute and Dr. Robert L. Coleman, Professor & Ann Rife Cox Chair for Gynecology, Division of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, conducted the workshop.

CA 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 provides information about the biological state of a disease (ovarian cancer) and is obtained by a blood sample from which a level can be measured. But it is more accurately considered a “tumor associated protein” because elevated CA 125 levels do not always indicate ovarian cancer and levels can misrepresent a biological state. For instance, CA 125 can be absent when disease is present, or levels can be high when no disease or no malignant disease exists. In addition, two patients with the same level can have widely different disease burdens. As you'll see or have personally experienced, this is certainly the case for ovarian cancer patients. Nevertheless, as a tool, serial changes in CA 125 levels, if elevated, can be fairly representative of disease status and frequently very helpful in the assessment of women with ovarian cancer.

THE CA 125 TEST

The current CA 125 blood test is the second generation of the test that was first introduced in the early 1980's 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, creative 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.

Early studies quickly identified that as many as 85% of women with ovarian cancer have elevated values; and, less than 1% of women without cancer have elevated levels of CA 125. However, there are notable exceptions: about 50% of Stage I ovarian cancer patients have normal values and the majority of patients with a certain tumor cell type called mucinous ovarian cancers have normal values. In addition, variations between patients may be substantial even if they have very similar tumors and, even within the same patient, variations can occur that are unrelated to the course of the cancer, particularly following surgery or if there is an infection.

So, the CA 125 test is helpful, but not perfect. Individual values are hard to interpret, so many physicians focus on the trend in the values over a course of time rather than 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 cells, 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 blood stream from specific organs, conditions that “perturb the silence” 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, non-cancerous 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), 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.

THE USE OF THE CA 125 TEST IN MANAGING THE CARE OF WOMEN WITH OVARIAN CANCER

The CA 125 test is used in a variety of situations during the course of the 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 for women with ovarian cancer and closely related cancers, such as fallopian tube and primary peritoneal cancer.
- **Detection:** CA 125 is widely employed to detect recurrent ovarian cancer in women who have been previously treated.
- **Monitoring:** CA 125 is used throughout the course of chemotherapy 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 in multianalyte platforms to help determine the risk of a malignancy preoperatively.

1. TO PREDICT OUTCOME

While more study is needed to completely determine how well a CA 125 test can predict the outcome of cancer treatment, several recent studies have looked at this question. If, during the first time a woman is treated for ovarian cancer, her CA 125 level returns to “normal,” does this mean that she will have a better chance of survival?

The answer seems to be “yes,” but with a note of caution. This conclusion only seems to be true when looking at the trends for large groups of women. CA 125 levels do not work as well as a predictor for individual women.

2. TO DETECT RECURRENT DISEASE

The CA 125 test is most reliable and useful for the detection of recurrent disease in women previously diagnosed and treated for ovarian cancer. While there are certainly exceptions to this statement, generally, rising numbers over a series of tests strongly suggest that a woman is experiencing a recurrence of her disease. However, some women develop a recurrence without a rising CA 125 level. On the other hand, some women have a modest rise in the value but never develop recurrent disease.

Recent evidence has suggested that using CA 125 to diagnose recurrent disease sooner does not result in an overall improved survival. Furthermore, following these values more closely caused physicians to administer more chemotherapy, thus causing a worse quality of life without improving outcomes. The role of CA 125 in the setting of detecting recurrent disease should be discussed with your doctor.

3. TO MONITOR TREATMENT

The CA 125 test is a generally reliable tool to use along with a thorough history and physical exam to assess or monitor if a treatment is working. However, its usefulness in this case depends on the starting value. Monitoring treatment results is most accurate when patients have an elevated initial CA 125 value. Some newer information is emerging suggesting that the trends of 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 fact 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 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 over-interpret 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 still will go on to respond to these drugs upon continued administration. Some patients even had a CA 125 rise after their second or even 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.

4. TO SCREEN FOR OVARIAN CANCER

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 for this cancer are variable, many women are diagnosed at a later, less treatable stage.

Therefore, there is much effort 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 ultrasound led to an increase in adverse outcomes relative to those women who did not get screening because the abnormal test results led to surgical procedures, which were not necessary. As explained earlier, there are many factors that influence “the number,” making it unreliable as a screening test for ovarian or any other reproductive cancer. The test misses up to 50% of those with early ovarian cancer 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 pre-menopausal women because both ovulation and menstruation can cause elevated levels.

However, research is ongoing to look at 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 either 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 elevating values. But it is still too early to know if this approach will prove beneficial in terms of cost and lives saved for the general population.

5. TO TRIAGE MASSES

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 included as one of several marker 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.

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. (Rodriguez, N Gyn Onc 2012). Additionally, CA 125 can be used in dynamic modeling to assess efficacy of new drugs in early development (Wilbaux N Gyn Onc 2014)

A FINAL NOTE

We urge women diagnosed with ovarian cancer to try to keep in mind that the CA 125 test is only one indication of how well the treatment is working.

Gynecologic oncologists, obstetrician-gynecologists with an additional three to four years of training in the comprehensive treatment of women with gynecologic cancers, are specifically knowledgeable about how to interpret what a CA 125 test result means in the treatment of ovarian cancer.

For information on how to find a gynecologic oncologist, and general information about ovarian and other women's cancers, please visit foundationforwomenscancer.org.

This award-winning Web site also has a section on clinical trials. The Gynecologic Oncology Group (GOG), a non-profit cooperative group that conducts most clinical trials related to reproductive cancers, is working with the Foundation to make information about clinical trials currently accepting enrollment readily available to women. Each trial is described and contact number given for the individual responsible for clinical trial enrollment at each institution participating in the trial.

For more information on ovarian and other gynecologic cancers, please call or e-mail the Foundation for Women's Cancer at 312.578.1439 or info@foundationforwomenscancer.org.

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Gynecologic Cancer
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Foundation for Women's Cancer
230 W. Monroe St., Suite 2528
Chicago, IL 60606-4902
Phone: 312.578.1439 Fax: 312.578.9769

info@foundationforwomenscancer.org
foundationforwomenscancer.org

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