



U N D E R S T A N D I N G C A 1 2 5 L e v e l s

A GUIDE FOR OVARIAN CANCER PATIENTS

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Society of Gynecologic Oncologists established the Gynecologic Cancer Foundation (GCF) in 1991 to develop educational programs for women, and create awareness about the prevention, early detection and treatment of gynecologic cancers. The Foundation also supports research and training related to gynecologic cancers.

As a 501(c)(3) not-for-profit charitable organization, GCF 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 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 Gynecologic Cancer Foundation. Dr. Thomas J. Herzog, Director, Division of Gynecologic Oncology, Columbia University, and Dr. Robert L. Coleman, Professor, 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 be misleading. For instance, CA 125 can be absent when disease is present, or levels can be high when no disease or no malignant disease exists. Therefore, CA 125 levels are interpreted with other markers of disease in mind including symptoms, physical exam findings, and imaging results such as pelvic ultrasound or CT scan.



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) 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 cut-off 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. This means that in the presence of an ovarian mass, a normal CA 125 does not necessarily mean that the ovarian growth is benign. 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.

Four primary roles for CA 125 assessment have been established with varying degrees of clinical use and reliability. The four 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.



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.



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 trends makes the test useful in treating ovarian cancer for the first time. Trending CA 125 values over time may also be useful in women undergoing treatment for disease recurrence. The most common non-platinum and non-taxane novel agents used in recurrent disease treatment, pegylated liposomal doxorubicin (Doxil) and topotecan (Hycamtin), require thoughtful interpretation of CA 125 levels during treatment. A significant number of patients ultimately responding to these drugs can have a rise in their CA 125 values — as much as 30% — after their first cycle of chemotherapy. Some patients even had a CA 125 rise after their second or even third cycle, and still had a favorable treatment outcome. 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 curable stage. Successful screening/early detection could change this fact dramatically. So it's no wonder there has been such a concerted investigational effort into strategies that could achieve this goal.

Unfortunately, the CA 125 test in isolation has proven to be ineffective in screening for ovarian cancer. 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 some promise is the use of a “cocktail,” or panel of markers (also known as “biomarkers”), and evaluating their changes, over time and in relation to each other. Several new biomarkers, like the HE4 protein, are being looked at in combination with CA 125, to see if they can improve upon the ability to catch the disease early, or at least reduce the number of women who are referred for surgery because of an abnormal test. This is also known as a “false positive screen” and is a problem with using limited information, like a single CA 125 value, in making a decision to further investigate the abnormal result. While this makes a lot of sense, it is still too early to know if this approach will prove beneficial in terms of cost and lives saved.



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. Many other variables need to be considered, and the applications of CA 125 values need to be individualized. Gynecologic oncologists are obstetrician-gynecologists with an additional three to four years of training in the comprehensive treatment of women with gynecologic cancers and 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 the Women's Cancer Network Web site (www.wcn.org).

This award-winning Web site of the Gynecologic Cancer Foundation (GCF) 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 GCF to make information on Phase III clinical trials currently accepting enrollment readily available to women. Each trial is described and women are offered the opportunity to call GOG at 1.800.225.3053 to learn how to reach the individual responsible for enrolling women in the nearest trial.

For more information on ovarian and other gynecologic cancers, please call or e-mail the Gynecologic Cancer Foundation at 312.578.1439 or info@thegcf.org. The GCF Hotline can be reached by calling 800.444.4441.



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