CA-125 Concentrations in Malignant and Nonmalignant Disease

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The patients in the cases presented here exhibit grossly increased CA-125 concentrations, yet have markedly different diagnoses. The second case raises the question of what, if any, concentration of CA-125 can be considered diagnostic of a malignant process. In the discussion that follows the presentation of cases, we review briefly the utility of CA-125 in formulating a diagnosis and in monitoring malignancies of the female reproductive tract. We then focus on the various nonmalignant conditions that may result in increased concentrations of CA-125 and how this affects interpretation of CA-125 test results.

Presentation of Cases

Case 1

The patient is a 43-year-old white woman admitted to Barnes Hospital for evaluation of a pleural effusion. She was in good health until three months before admission, when she developed right pleuritic chest pain accompanied by a nonproductive cough. A chest roentgenogram at that time showed a right pleural effusion. A computed tomography (CT) scan of the chest revealed only granulomatous disease. However, a subsequent chest roentgenogram one week before admission demonstrated increased pleural effusion; consequently, the patient was admitted. Physical examination on admission was remarkable only for a rub over the right lung base; results of abdominal and pelvic exams were within normal limits. Admitting laboratory evaluations, including complete blood count, urinalysis, serum electrolytes, amylase, and antinuclear antibodies were within normal limits, and a tuberculin test was not reactive. The patient's erythrocyte sedimentation rate was slightly above normal at 32 mm/h (reference range = 0–20 mm/h).

After admission, a ventilation perfusion scan was performed, which showed matched ventilation–perfusion defects. Pleural fluid obtained by diagnostic thora-

cocentesis was consistent with a malignant exudate containing adenocarcinoma. CT of the pelvis revealed an enlarged uterus and a 2-cm right adnexal mass. The concentration of CA-125 was 387 units/mL (reference range, 0–16 units/mL).

The patient underwent exploratory laparotomy, which confirmed Stage IV ovarian cancer. A total abdominal hysterectomy and oophorectomy were performed. Histologic examination of the right ovary demonstrated poorly differentiated adenocarcinoma. The patient subsequently was treated with a series of cis-platinum-based cytotoxic chemotherapy with good response. Follow-up examinations revealed no evidence of disease recurrence. The patient's CA-125 concentration decreased from 241 units/mL after surgery to 10 units/mL after chemotherapy. However, about 15 months later, at a routine checkup, the patient's CA-125 concentration was found to be increased to 122 units/mL and peritoneal washings revealed adenocarcinoma. The patient was recommended for radiation ablation and subsequent bone marrow transplantation.

Case 2

The patient is a 49-year-old white woman with a two-month history of ascites, admitted to Barnes Hospital for evaluation. Laboratory tests performed on admission showed an alkaline phosphatase (EC 3.1.3.1) concentration of 154 U/L and a y-glutamyltransferase (EC 2.3.2.2) of 58 U/L (reference ranges, 35–100 and 4–32 U/L, respectively). Aspartate aminotransferase (EC 2.6.1.1), lactate dehydrogenase (EC 1.1.1.27), and creatine kinase (EC 2.7.3.2) were within normal ranges. The patient's leukocyte count was 14.8 × 10^9/L, with 80% granulocytes. Tests performed one month earlier were similar. A liver–spleen scan revealed an inhomogeneous liver with a small right lobe and a colloid shift to spleen and marrow, indicating liver cirrhosis. Abdominal and pelvic CT revealed large amounts of ascites, with focal enhancement of the peritoneal membrane in the cul-de-sac. Pelvic ultrasound results were normal. Routine, anaerobic, and fungal cultures, as well as acid-fast bacilli of ascitic fluid, were negative.

Nineteen days after admission, the patient underwent diagnostic laparoscopy, during which 1500 mL of nonpurulent ascitic fluid was removed. The examination revealed normal-appearing uterus, fallopian tubes,
and ovaries; a cul-de-sac mass of approximately $2 \times 4$ cm of white mucoid material; multiple areas of this white mucoid material on the peritoneum near the left ovary and on appendices epiploics of the sigmoid colon; and a small liver with firm gray texture. Biopsies were taken from liver and the masses for pathological examination. Measurement of serum CA-125 was ordered, and was found to be 860 units/mL (reference range, 0–16 units/mL). To rule out the surgical procedure as a cause for false increase in CA-125 concentrations, a preoperative sample was analyzed for CA-125 which was found to be 1070 units/mL.

The liver biopsy revealed evidence of chronic active hepatitis, probably secondary to virus or drug use. Biopsies from the masses revealed evidence of necrosis and acute inflammation, with no evidence of malignancy. The patient was discharged three days after surgery, and was placed on a sodium-restricted diet and spironolactone. Corticosteroid therapy was withheld until the absence of malignancy was confirmed.

Laparotomy was considered to rule out malignancy if the CA-125 concentration did not regress. One month later, the CA-125 concentration was 8 units/mL.

Discussion

Malignancies of the female reproductive tract constitute ~28% of malignant tumors in women, and ~75 000 new cases are diagnosed each year in the U.S. (1). Ovarian carcinoma represents 20–25% of the newly diagnosed cancers of the female genital tract each year, and has a mortality rate of 11 000 per year, the highest among female genital tract malignancies (1). Earlier detection is needed because 75% of new ovarian carcinomas are diagnosed at Stages III or IV, which have poor five-year survival rates (1).

Since the discovery of the oncofetal antigens carcinoembryonic antigen (CEA) and α,1-fetoprotein in the 1960s, extensive research has been directed toward identifying markers of human malignancies. Several tumor markers, including CEA and α,1-fetoprotein, have utility for prognosis, monitoring therapy, and detection of recurrences of malignancy, but few have proven useful for initial diagnosis (2). Although specific and sensitive markers exist for some female reproductive tract malignancies such as trophoblastic neoplasias and cervical cancer (β-human chorionic gonadotropin and Pap smear, respectively), similar tests have not been available for ovarian carcinoma. Many antigens have been examined as potential tumor markers to aid in diagnosis and monitoring of ovarian carcinoma, including human placental lactogen, CEA, placental alkaline phosphatase, ovarian carcinoma antigen, CA 50, and CA 19-9, but none have proven to have sufficient specificity or sensitivity in routine clinical applications (3, 4). In 1981, the antigen CA-125 was identified by Bast et al. (5) on ovarian carcinoma cells by using the monoclonal antibody OC 125, and CA-125 was proposed as a specific marker of ovarian carcinoma.

The CA-125 molecule. The CA-125 molecule is a 200-kDa glycoprotein, initially identified on the surface of the ovarian carcinoma cell line OVCA 433 (5). In serum, the molecule is found in multiple molecular mass forms ranging from 200 to 1000 kDa (6). The molecule contains ~25% carbohydrate, but the monoclonal antibody used in commercial immunoassays, named OC 125, is thought to detect a protein epitope (6). The CA-125 molecule is widely distributed on the surface of both healthy and malignant cells of mesothelial origin, including pleural, pericardial, peritoneal, and endometrial cells, as well as in the normal genital tract (7) and amniotic membrane (8). The highest concentrations of CA-125 in normal body fluids occur in uterine, cervical, and amniotic fluid (7, 9). CA-125 has also been identified on tissues of nonmesothelial origin, such as tracheobronchial epithelium, amniotic tissue, and cervical mucous membrane. Interestingly, the molecule is not present on the surface of normal fetal or adult normal ovarian cells, but is present on >80% of malignant ovarian tissue of nonmucinous origin (10). Neither the gene for nor the function of CA-125 has yet been identified. The CA-125 antigen is present at low concentrations (<35 units/mL) in the serum of healthy males and females.

Assays of CA-125. Since development of the original RIA of CA-125, commercial immunoradiometric assays (IRMA), enzyme immunoassays (EIA), and most recently an immunoluminometric assay (ILA), have been developed and marketed. These assays are based on the double-antibody sandwich principle and involve the monoclonal antibody OC 125 for both capture and detection. Both the commercial EIA and IRMA involve CA-125 purified from the OVCA 433 cell line as standards (10, 11). Nevertheless, the two assay configurations have been shown not to produce identical results. Linear regression performed on 60 samples assayed by both methods revealed the following relationships: CA-125/EIA = 0.75 × CA-125/IRMA − 7.9 (r = 0.95) in one study (11), and CA-125/EIA = 0.82 × CA-125/IRMA − 12 in another (12). Thus, deviation of the slope of the regression line from 1.0 results in different reference ranges and cutoff values for the two assays, which must be recognized when examining the literature. For instance, the cutoff values frequently referred to of 35 or 65 units/mL by IRMA correspond to 16–18 or 41 units/mL by EIA (11, 12). One potential limitation of the EIA is a detection limit of 12 units/mL, compared with 1.4 units/mL for the IRMA (11), which may limit the utility of the EIA for early detection of recurrence of malignancy in patients after surgery. The presence of a “matrix effect” in the CA-125 assay that affects the accuracy of extremely high values determined with diluted samples was described in an announcement to users from the manufacturer of the EIA (Abbott Labs., North Chicago, IL) in January 1990. Values determined with diluted samples can be greater than the value of an undiluted sample; to minimize this effect, the manufacturer recommended a standard dilution scheme. It is especially important to use a standardized dilution scheme when monitoring serial values from a single patient. Nevertheless, because the sample from
Case 2 was >650 units/mL undiluted, it is clear that this patient had a markedly increased CA-125 concentration. Finally, regression analysis of the ILMA assay revealed the following: ILMA = 0.92 × IRMA + 1.06 (r = 0.97) (13).

CA-125 and Malignancy

Utility for screening. In the initial report of the CA-125 IRMA, 888 apparently healthy blood donors (537 men, 351 women; median age 34 years) were examined and a normal serum value for CA-125 of <35 units/mL was established (10). Serum CA-125 concentrations >35 units/mL were found in 1% of the group, and values >65 units/mL were present in 0.2%. There was no difference by gender in the number of samples with increased values. Another study of 915 apparently healthy women with a median age of 55 years demonstrated values >65 units/mL in 0.3% of the samples (14). Studies of women with confirmed nonmucinous ovarian carcinoma demonstrated increased CA-125 concentrations (>35 units/mL) in 80–85% of the cases (10). However, not all studies classified the patients according to the stage of disease. This is important because studies of patients with Stage I and II nonmucinous ovarian carcinoma, when diagnosis is most important for effective therapy and good prognosis, showed that only <10% had CA-125 concentrations >35 units/mL (10, 14). Furthermore, even if one assumes a 100% sensitivity for the test, a 35 units/mL cutoff (99% specificity) would result in 1000 positive results in 100,000 tests. However, given an incidence for ovarian cancer of about 20 cases per 100,000 women, only 20 of these cases would be true positives and the positive predictive value would be 2%. Thus, CA-125 measurement alone is not suitable as a screening test of the general population.

The low positive predictive value of CA-125 for ovarian carcinoma stands in contrast to the tumor marker prostate-specific antigen (PSA) that has been reported useful as a screening test for prostatic adenocarcinoma. In a recent study of 1653 randomly recruited men ages 50 years and older, PSA was found to have a specificity of 95% and a positive predictive value of 33% for biopsy-proven prostate cancer (15). The difference between the positive predictive values of these two tumor marker assays lies not in assay performance, but rather in the incidence of the respective tumors. In the same study, the incidence of biopsy-proven prostate cancer was 2.2% (15), whereas others state an incidence as high as 10% for men in their 50s that increases to 70% for men in their 80s (16). The difference in the positive predictive value of these two tumor markers serves as an excellent reminder of how the incidence of disease affects predictive values of laboratory tests.

Confirmatory or multiple tests can increase the predictive value of some tumor markers. For instance, the use of a rectal exam or ultrasonography to confirm a positive PSA value improved the positive predictive value in the above study to 38% (15). Recent studies have examined the use of independent tumor markers as confirmatory markers for positive CA-125 results in ovarian carcinoma. In a preliminary study, 80% of patients with ovarian tumors who had increased CA-125 concentrations also had increased concentrations of CA 15-3 or TAG 72.3, whereas <5% of patients with falsely increased CA-125 concentrations were also positive for these markers (17). In another study, concurrent increase in CA-125, CA 15-3, and TAG 72 improved diagnostic specificity to 99%, but decreased sensitivity for differentiating between malignant and benign pelvic lesions (18). Finally, combining CA-125 measurement with CA 19-9, tissue polypeptide antigen, and immunosuppressive acidic protein has been demonstrated to increase sensitivity for predicting recurrence in patients with recurrent ovarian carcinoma (19). Such studies suggest promise for early detection of ovarian carcinoma by making use of a multiple test algorithm, but these results clearly need to be confirmed and expanded.

Use of CA-125 in differential diagnosis. Although proposed initially as a marker for ovarian carcinoma, it is now clear that other reproductive tract malignancies also result in increased concentrations of CA-125. For instance, a study of 60 women with various nonovarian tumors demonstrated increased CA-125 concentrations in 100% of those with fallopian tube tumors, 83% with cervical adenocarcinoma, 50% with endometrial adenocarcinoma, but in <15% of patients with squamous cell tumors of the vulva or cervix (14). Another study found CA-125 concentrations >35 units/mL in sera of 94% of patients with epithelial ovarian tumors. CA-125 concentration was also increased in endometrial adenocarcinoma, cervical squamous cell carcinoma, and colorectal adenocarcinoma in 47%, 20%, and 32% of the cases, respectively. Trophoblastic tumors caused increased CA-125 in 45% of the patients (20). Thus, CA-125 can be increased in many female reproductive tract malignancies in addition to OVCA, and is not useful for the differential diagnosis of female genital tract tumors of unknown origin.

CA-125 for monitoring therapy of ovarian carcinoma. Like many other tumor markers, CA-125 has proven most useful for monitoring therapy and predicting tumor recurrence. In an earlier study Bast et al. (10) demonstrated that, in patients positive for CA-125 before therapy, an increase or decrease in CA-125 correlated with the clinical course (Figure 1). In this study, a twofold increase or decrease in concentrations of CA-125, but not in CEA, during therapy was shown to be significant. Another study examined 62 women with nonmucinous ovarian carcinoma who underwent "second-look" surgery not based on their CA-125 values (21). Of these women, 12 had increased CA-125 concentrations at the time of second-look surgery and persistence of tumor was documented in all 12 patients. In contrast, negative results did not indicate the lack of recurrent or persistent tumor, because 19 patients with persistent tumor had CA-125 concentrations <35 units/mL. All 24 women with no surgical evidence of persistent tumor were negative for CA-125. Thus, CA-125 determination in this setting is a "one-way" test (i.e., increased concentrations indicating tumor recurrence, but negative findings having little
predictive value). The value of positive findings was further emphasized in a report of several cases in which an increase in CA-125 was an earlier indicator of retroperitoneal lymph node metastasis than was routine clinical monitoring or laparoscopy (22). Taken together, these findings demonstrate the value of CA-125 measurement as a noninvasive diagnostic tool for detecting early tumor recurrence or persistence. The patient in Case 1 represents a typical pattern in CA-125 values. Initially increased during her disease, the CA-125 concentrations of the patient decreased after tumor ablation by surgery and chemotherapy. Unfortunately, this patient exhibited a recurrence of her tumor, and CA-125 values reflected this.

CA-125 in nonmalignant disease. Differentiating benign from early malignant disease of the female reproductive tract is an important but often difficult diagnostic dilemma. A study by Einhorn et al. (23) suggested that CA-125 would be useful for differentiating malignant from benign pelvic masses. In this study, 100 patients with diagnoses confirmed by laparotomy were examined. Of 23 patients with ovarian (n = 18) or other malignant adnexal tumors (n = 5), 19 had CA-125 concentrations >35 units/mL measured by IRMA. In contrast, only five of 77 patients with benign conditions had increased CA-125 concentrations. These increases were generally slight to moderate, ranging from 40 to 200 units/mL, and were observed in patients with acute pelvic inflammatory disease, benign neoplasms, and endometriosis. Although increased concentrations of CA-125 were present in only 6% of those with benign conditions, this raised the possibility that certain benign conditions may result in increased CA-125 concentrations. Nevertheless, one study stated that CA-125 concentrations >110 units/mL have always been associated with malignant disease and that values >200 units/mL were almost always indicative of ovarian carcinoma (24). In Case 2 presented here, the patient had grossly increased CA-125 concentrations (860 and 1070 units/mL), but a malignant process was very low in the differential diagnosis. This prompted questions to the laboratory medicine resident as to what concentrations are diagnostic of malignancy. Therefore, we examined the literature to determine what, if any, nonmalignant diseases could result in serum CA-125 concentrations approaching those observed in Case 2. This survey of the literature is summarized in Table 1 and is discussed below.

CA-125 in conditions affecting the endometrium. Both pathological and normal physiological changes in the endometrium, e.g., menstruation and pregnancy, have

Table 1. Some Benign Conditions Associated with Increased CA-125 Concentrations

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients</th>
<th>No. %</th>
<th>Highest value, units/mL</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstruation</td>
<td>28</td>
<td>10</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>15</td>
<td>3</td>
<td>72</td>
<td>25</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>8</td>
<td>7</td>
<td>103</td>
<td>24</td>
</tr>
<tr>
<td>Benign pelvic masses</td>
<td>153</td>
<td>61</td>
<td>&gt;400</td>
<td>31</td>
</tr>
<tr>
<td>Lung and pleural diseases</td>
<td>60</td>
<td>21</td>
<td>270</td>
<td>34</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>24</td>
<td>13</td>
<td>200</td>
<td>35</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome</td>
<td>30</td>
<td>10</td>
<td>550</td>
<td>36</td>
</tr>
<tr>
<td>Fibroma + Meigs</td>
<td>1</td>
<td>1</td>
<td>669</td>
<td>29</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>14</td>
<td>12</td>
<td>900</td>
<td>41</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>66</td>
<td>44</td>
<td>5000</td>
<td>37</td>
</tr>
<tr>
<td>Chronic liver disease (no ascites)</td>
<td>16</td>
<td>6</td>
<td>220</td>
<td>42, 43</td>
</tr>
<tr>
<td>Liver cirrhosis and ascites</td>
<td>15</td>
<td>15</td>
<td>800</td>
<td>42</td>
</tr>
</tbody>
</table>

* Endometriosis + adenomyosis.

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been shown to increase serum CA-125 concentrations in some women (25). When CA-125 concentrations in 28 normal menstruating and 15 pregnant women (26–32 days after last menses) were examined, two cases of increased CA-125 in a menstruating subject and a pregnant subject (65 and 72 units/mL, respectively) were identified (25). Underlying pathology was ruled out in both patients by laparotomy. Another study examined 20 apparently healthy first-trimester pregnant women and found four cases of increased CA-125, ranging from 65 to >500 units/mL (20). Thus, in one apparently healthy pregnant patient, CA-125 concentrations approached those seen in our Case 2. However, in this study the means of ruling out a hidden pathology were not reported. Nevertheless, it seems clear that normal pregnancy can increase serum CA-125 values, at least moderately.

Although pregnancy and normal menses do not often present a diagnostic problem, it is important to rule out benign endometrial disease as a cause of high CA-125 concentrations when considering the diagnosis of female reproductive tract malignancy. Numerous studies have examined serum CA-125 values in patients with endometriosis and reported it to be increased (4, 23–29). The degree of increase was claimed to correlate with the severity of endometriosis in some studies (25, 26, 28). For instance, one study of 130 women found increased concentrations of CA-125 in 27%, 68%, 73%, and 100% of patients with minimal, mild, moderate, and severe endometriosis, respectively (25). The highest value observed in these patients was 109 units/mL. Giudice et al. (24) also reported increased serum CA-125 in seven of eight women with surgically confirmed Stage II or III endometriosis, with the highest value being 103 units/mL, prompting the conclusion that concentrations of CA-125 >200 units/mL were diagnostic of malignancy (24). These and other studies (4, 26–29) clearly demonstrate that moderately increased (≤200 units/mL) serum CA-125 is frequently observed in advanced stages of endometriosis, although the mechanism is unclear (30), and suggest limitations of using CA-125 values for differentiating benign from malignant processes.

In addition to these moderate increases in CA-125, several isolated cases of marked increases associated with endometriosis have been reported (4, 26, 29). One study of 34 women with endometriosis identified two patients with concentrations of 390 and 690 units/mL (26). Interestingly, both of these women had associated adenomyosis, but malignant disease was ruled out by laparotomy or laparoscopy. Other studies have reported endometriosis or adenomyosis patients with CA-125 concentrations as high as 400–740 units/mL (4, 29, 30). Moreover, when CA-125 concentrations were examined in 21 patients with laparotomy-confirmed adenomyosis, 16 had increased CA-125 values with a mean value of 233 ± 72 units/mL (27). Thus, in addition to relatively moderate increases in CA-125 in benign endometrial disease, extreme increases near those observed in Case 2 presented here can occur without a malignancy. Although the above pathological and physiological conditions were not part of the differential diagnosis in Case 2, they point out the limited value of CA-125 measurement in differentiating benign from malignant conditions, even at CA-125 concentrations as high as 500 units/mL.

CA-125 in benign neoplasm. One of the most difficult diagnoses in the absence of biopsy is the differentiation of benign from early malignant pelvic masses or cysts. Unfortunately, two well-documented studies showed that CA-125 determinations are of little value in this differentiation. Among 59 patients with histologically proven benign neoplastic cysts, 12 had CA-125 concentrations >35 units/mL, four with >65 units/mL, and one with near 2000 units/mL (4). In another study, 10 of 153 women with benign pelvic masses diagnosed by surgery or physical examination had CA-125 concentrations >188 units/mL and one patient had a value >400 units/mL (31). Particularly disturbing is a report of two women with a presumptive diagnosis of ovarian carcinoma based on CA-125 concentrations of 690 and 1200 units/mL, who proved to have benign ovarian cysts at laparotomy (32). Thus, very high CA-125 concentrations (i.e., >1000 units/mL) have been observed in proven benign conditions and such values should not be considered an absolute indication of malignancy.

CA-125 in benign lung and pleural diseases. Because CA-125 is expressed on normal pleural mesothelial tissue, increases in CA-125 concentrations might be expected in cases of pleural irritation (33). Several studies demonstrated increased CA-125 in patients with nonmalignant lung disease. Two studies of 60 and 34 patients found increased CA-125 values in 26% and 38% of the patients, respectively, with values as high as 270 units/mL (34, 35). These patients had various conditions, including bronchial asthma, bronchial pneumonia, chronic obstructive pulmonary diseases, and congestive heart failure, but all had pleural inflammation or effusions. No relation was found between patient gender and the CA-125 increase. Although pulmonary disease was not part of the differential for Case 2, these studies demonstrate that irritation of tissues where CA-125 is normally expressed can result in high serum concentrations, approaching those generally associated with malignancy.

CA-125 in pelvic inflammatory disease and peritonitis. Because the CA-125 molecule has been identified on normal peritoneal and fallopian tube tissue (36), it is not surprising that inflammation of these tissues can result in increased concentrations of serum CA-125. An early study found that nine of 12 women with suspected peritonitis had CA-125 concentrations >65 units/mL, with two patients having values >500 units/mL (37). A more definitive study examined CA-125 values in 30 patients with pelvic inflammatory disease associated with fever who had good response to antibiotic therapy (36). CA-125 was >100 units/mL in five patients (17%) and the highest value was 550 units/mL. A recent study of 33 patients with acute pelvic inflammatory disease
showed 32 to have increased concentrations of CA-125, with values between 100 and 1300 units/mL (38). Interestingly, in some studies the degree of CA-125 increase appeared to correlate with the extent of salpingitis, but not with the isolated organism (38). Thus, inflammatory reactions of the peritoneum can also result in marked increases in CA-125, and it is possible that the increased serum concentration is secondary to local expression of CA-125 by the inflamed tissue.

On the basis of such studies, it has been hypothesized that, in peritonitis, lymphatic drainage of peritoneal fluid rich in locally produced CA-125 results in increased serum CA-125 (39), and this may account for some or all of the increase in CA-125 in Case 2. The low concentration measured at the last hospital visit of Case 2 followed a prolonged course of antibiotics and was associated with the total disappearance of all clinical signs and symptoms of peritonitis.

**CA-125 in conditions associated with ascites.** Several other benign conditions have been reported to increase serum CA-125 concentrations. Although not related, these conditions share a feature of producing ascites during their later stages. In one study, Jäger et al. (7) measured serum CA-125 in 16 patients stimulated with exogenous gonadotropin during preparation for in vitro fertilization. Nine patients showed a marked increase in CA-125 concentrations—ranging from 200 to 500 units/mL—during the course of treatment; all were diagnosed as having ovarian hyperstimulation syndrome on the basis of clinical and ultrasonographic examination, with cystic enlargement of the ovary and the presence of ascites and pleural effusion. In this group of patients, the increase in CA-125 appeared to be solely a consequence of ovarian hyperstimulation syndrome, because normal CA-125 values were found in the seven other patients who failed to develop signs of ovarian hyperstimulation. Fukazawa et al. (29) also reported one case of ovarian hyperstimulation with a CA-125 concentration of 669 units/mL. In a third study including 56 patients with pelvic masses, three cases were diagnosed as having fibroma, with and without Meigs syndrome. All three had increased CA-125 concentrations, ranging from 300 to >1000 units/mL; however, the presence of ascites could not be determined from the report (40). Again, although not part of the differential diagnosis for Case 2, these conditions demonstrate how certain benign conditions associated with irritation of the ovaries or the peritonium and resulting in ascites can cause marked increases in serum CA-125.

Further association between ascites and increase in concentrations of CA-125 has been found in chronic liver diseases and cirrhosis. In a study of 14 patients with alcoholic liver cirrhosis, Ricolleau et al. (41) reported 10 patients with CA-125 concentrations >100 units/mL, six with values >500 units/mL, with the highest value approaching 900 units/mL. Ruibal et al. (37) also reported that 28 of 66 cases with chronic liver diseases had CA-125 values >200 units/mL, and 10 patients had values between 500 and 5000 units/mL. Some studies correlated the appearance of ascites to increases in CA-125 by examining two groups of patients with chronic liver cirrhosis (42, 43). The first group had no ascites (n = 16); the second group had ascites and cirrhosis (n = 39) as confirmed by echography and paracentesis. Only two patients in the first group had CA-125 >100 units/mL, whereas 32 of 39 patients in the second group had CA-125 values ranging from 100 to 800 units/mL (42, 43). Causes of cirrhosis in the two groups were alcohol, chronic active hepatitis positive for hepatitis B surface antigen, primary biliary cirrhosis, and cryptogenic cirrhosis. Mezger et al. (44) also studied CA-125 in 15 patients with ascites from benign conditions (liver cirrhosis and congestive heart failure) and found that their CA-125 concentrations ranged from 133 to 1837 units/mL.

Thus, there apparently is a relationship between ascites and an increase in CA-125 in serum, and furthermore the increase is independent of the nature of the original pathology or the affected organ. Because CA-125 is probably cleared by the liver, increases in CA-125 possibly are aggravated in patients with liver diseases (44). However, it is more logical to attribute this increase to involvement of the peritoneum, where CA-125 is normally expressed. Evidence supporting this assumption is that the concentration of CA-125 in ascitic fluid correlates with, but exceeds, the corresponding serum concentrations and that paracentesis dramatically and rapidly decreases concentrations of CA-125 in serum (45–47).

The close relationship between the development of ascites and the increases in serum CA-125 is compatible with the etiology of the highly increased serum CA-125 in Case 2. At the time of increased CA-125 measurement, the patient had a large ascites and a picture of peritoneal inflammation. After the removal of 1.5 L of ascites, along with antibiotic treatment of the peritoneal inflammation, the patient's serum CA-125 returned to normal.

**Summary**

CA-125 is a high-molecular-mass glycoprotein expressed on the cell surface of some derivatives of embryonic coelomic epithelium. This tumor-associated antigen widely used to monitor ovarian carcinomas has been suggested as a promising noninvasive test that could differentiate benign from malignant conditions. Based on results of various studies, CA-125 measurement appears to be very useful in monitoring the response to therapy of ovarian carcinoma and for detecting tumor recurrence as exemplified in Case 1. However, because of the high frequency of false-positive results associated with many benign conditions, CA-125 is of little value as a screening test for ovarian carcinoma. A brief list of the most common benign conditions associated with CA-125 increase includes menstruation, pregnancy, benign pelvic tumors, pelvic inflammatory diseases, ovarian hyperstimulation syndrome, peritonitis, and many diseases leading to pleural effusion or ascites. According to several studies, a marked increase in CA-125 of...
tumors.


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Jäger Malkasian Elevated levels of CA-125 in serum of patients suffering from ovarian hyperstimulation syndrome. Fertil Steril 1987;47:675-8.


