CA-125: A Biomarker Put to the Test

By Charlie Schmidt

In 1998, an e-mail beseeching women to undergo annual CA-125 screening for ovarian cancer spread across the Internet. “Please, please, p-l-e-a-s-e tell all your female friends and relatives to insist on a CA-125 blood test every year as part of their annual physical exams,” pleaded the note from a cancer patient. “Don’t take no for an answer.”

Unfortunately, the science behind CA-125 screening wasn’t ready for prime time then, and it still isn’t. In June, a National Cancer Institute–sponsored randomized study published its long-awaited results in the *Journal of the American Medical Association*. The findings showed that simultaneous CA-125 and vaginal ultrasound screening did not affect ovarian cancer mortality. But this study—the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, launched in 1993—used what some scientists say is an outmoded approach for tumor detection.

Meanwhile, a different study, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), is using a different screening approach that could be more promising, according to Ian Jacobs, director of the Manchester Academic Health Science Centre, in Manchester, United Kingdom, and one of the study’s principal investigators. Thus CA-125 screening, which some still see as perhaps the best hope for early ovarian cancer detection, remains in limbo.

**A Brief History**

CA-125 is a large transmembrane protein that ovarian and other cancer cells shed. Robert Bast, M.D., now vice president for translational research at the University of Texas M. D. Anderson Cancer Center, in Houston, discovered the protein in the early 1980s. Bast called the protein “cancer antigen 125” because it was recognized by the 125th monoclonal antibody produced against an ovarian cancer cell line. In a later study, using banked serum samples from Norway, Bast found that elevated CA-125 levels could occur months or even years before ovarian cancer was diagnosed. CA-125 has key roles in cancer cell motility and invasiveness.

Today, it’s used mainly to monitor the effects of chemotherapy.

Investigations into the protein’s value for cancer screening date back to the early 1990s. Around that time, Jacobs found that combining CA-125 analysis with vaginal ultrasound substantially improved screening specificity in cancer detection, reducing false-positive findings that could result from using each approach independently. Beginning in 1993, NCI launched PLCO, using an ovarian screening protocol that combined vaginal ultrasound with simultaneous CA-125 analysis, the latter pegged to a threshold of 35 IU/mL. A total of 78,216 postmenopausal women, aged 55–74 years, were randomly assigned to either standard medical care or an intervention arm in which they were referred to their primary-care doctors if their ultrasound results were abnormal (enlarged or cyst-containing ovaries) or if their CA-125 levels were above the 35-IU/mL cutoff. The protocol did not specify precisely how women and their doctors should respond to abnormal ultrasound or to elevated CA-125 levels. “Next steps could include repeat ultrasound, repeat CA-125, gynecological exam, or surgery,” said Saundra Buys, M.D., a principal investigator in the PLCO trial and a director at the Huntsman Cancer Institute, at the University of Utah.

When the trial wrapped up after up to 13 years of observation, 212 women from the intervention arm and 176 women from the control group had been diagnosed with ovarian cancer. But ovarian cancer mortality differences between the two groups weren’t statistically significant. A total of 118 deaths occurred in the intervention group, compared with 100 in the control group. According to Buys, that discrepancy probably reflects an “overdiagnosis bias” in the intervention arm. “Some of these cancers did not need to be diagnosed,” she said. “They weren’t going to cause death even if they weren’t detected.” That’s because, as also occurs in prostate and breast tumors, some ovarian cancers are slow growing and might be better left untreated, explains Christine Berg, M.D., chief of the NCI’s early detection research group. Moreover, CA-125 levels can rise in response to some benign conditions, including endometriosis, other ovarian diseases, and pregnancy. So, not only did PLCO’s screening approach not reduce mortality in ovarian cancer, it also led to many surgeries performed to investigate positive screening results. Of 3,285 women with false-positive results, 1,080 underwent surgical follow-up, and among them, 163...
women—15% in all—experienced at least one serious complication. “Some of those surgeries addressed other types of problems, so you can’t always call them unnecessary,” Buys said. “But we can say that screening the way we did it had no effect on survival, and it did result in surgeries for conditions that turned out not to be ovarian cancer.”

**PLCO versus the ROCA**

Buys, who emphasized that PLCO doesn’t mark the demise of CA-125 as a screening tool, said the UK trial perhaps had a more sensitive use of the protein to detect ovarian cancer. Whereas PLCO based its response on crossing a threshold—the 35-IU/mL cutoff—UKCTOCS bases its responses in part on how a woman’s CA-125 value changes over time. Normal CA-125 values can vary substantially among women: Values detected in healthy individuals can range from as low as 5 to more than 50 IU/mL, throwing the 35-IU/mL cutoff into question, according to Jacobs.

During the mid-1990s, Steven Skates, Ph.D., an associate professor of medicine at Harvard Medical School, and Jacobs collaborated on an algorithm (the Risk of Ovarian Cancer Algorithm, or ROCA) that estimates a woman’s risk of having ovarian cancer first as a function of age only (older women have higher risks) and then by integrating age risks with later CA-125 values. Screening decisions—for instance, referral to ultrasound—are then made using the risk estimate instead of the latest CA-125 value. The ROCA’s accuracy improves with every additional measurement, Skates said. With more than 200,000 postmenopausal women older than 50 years, UKCTOCS is the largest such trial using the algorithm. Several smaller early detection trials are also using it with different patient populations, including some at high risk of ovarian cancer on the basis of family history and/or BRCA1/2 status, Skates said.

According to Skates, the ROCA generates a pair of dynamic, population-based profiles: one describing CA-125 level changes before diagnosis in women with ovarian cancer and another describing baseline values for women who don’t have the disease. The more a woman’s CA-125 level resembles the first profile, the higher her risk of having ovarian cancer. If a woman’s risk is within the reference range, she returns for another CA-125 test in a year. If the changes look worrisome, but not too threatening, a woman returns for an additional CA-125 test after a few months, whereas more substantial increases lead to referral for ultrasound or surgery. According to Usha Menon, M.D., professor of gynecological oncology at University College London, by monitoring fluctuations in CA-125 level, clinicians can cut down on the number of surgeries otherwise triggered by crossing an arbitrary CA-125 threshold. In fact, preliminary UKCTOCS data indicate that ROCA leads to three surgeries for every detected case of ovarian cancer, which is far less than a ratio of 10:1, the minimal requirement specified in the literature, according to Bast. “Rising CA-125 is a much more specific indicator,” he said. “And that’s the primary difference the PLCO, which doesn’t take a patient’s own baseline into account.”

Bast current directs a smaller, single-arm study using the ROCA in postmenopausal women older than 50—excluding BRCA1/2 patients and others with strong familial risk—at the M.D. Anderson Cancer Center. The study now has 3,800 enrolled women. So far, the ROCA has prompted nine surgeries, resulting in five ovarian cancer diagnoses, two of them “borderline,” or not yet overtly malignant. “And among those five diagnosed cases, only one was symptomatic,” Bast said.

**Searching for Other Biomarkers**

Meanwhile, scientists are also looking for other ovarian cancer biomarkers in addition to CA-125. And along those lines, the PLCO has left a treasure trove of material. “That study gathered samples from women years before they were diagnosed,” Jacobs said. “So there’s a lot of sophisticated laboratory work being done on those samples now.”

Bast, in fact, is working with PLCO tissue samples to develop multibiomarker panels and antibodies that could potentially estimate cancer risk. The most diagnostically powerful panel, he said, consists of 23 biomarkers, including CA-125. He thinks that some of these markers will one day reside on a nanochip, which can deliver predictive estimates from a simple blood sample in a matter of minutes.

As for using CA-125 to assess treatment benefits now, a research article in this issue of the Journal suggests that the rate of CA-125 decline does not predict the likelihood of achieving a long-term response to therapy.

But Buys points out that this finding doesn’t negate that CA-125 is an effective predictor of relapse and treatment response. “In women previously treated for ovarian cancer and who have no current evidence of disease, a rising CA-125 [level] is a very sensitive predictor of relapse,” she said. “And CA-125 is also a good measure of response to therapy—if CA-125 falls, the tumor is responding. [The research article in this issue] makes the point that the rate of decline of CA-125 does not predict the likelihood of achieving a long response to therapy. In other words, women treated with one treatment regimen compared to a second treatment regimen took a longer time to have the CA-125 fall but had a longer duration of benefit. The article does not contradict that a dropping CA-125 corresponds to a response to therapy; it just demonstrates that the rate of drop does not predict the overall benefit.”

Dr. Bast has received royalties for CA-125 from Fujirebio Diagnostics Inc. He has also served on scientific advisory boards for Fujirebio Diagnostics, Vermillion, and Illumina. Dr. Ian Jacobs is co-inventor of ROCA, along with Steve Skates. He is also director and shareholder of Abkodia Ltd., and a consultant to Becton Dickinson for ovarian cancer screening.