Personalizing Ovarian Cancer Screening

By Merrill Goozner

Preliminary results from an ovarian cancer screening test that relies on personalized findings from an annual CA125 blood test are keeping alive hope that someday an effective screening tool for the disease may be a reality. But researchers warn that the method is not perfect and that proof that it decreases the risk of dying from the rare but deadly cancer is still several years away.

Researchers led by Karen Lu, M.D., of the M. D. Anderson Cancer Center in Houston, unveiled the results of the personalized screening method at the June meeting of the American Society of Clinical Oncology. A much larger randomized trial of the same method is now under way in the UK.

The M. D. Anderson trial involved giving annual blood tests that measured CA125 to 3,238 women aged between 50 and 74 over 8 years. But the screening test didn’t rely solely on higher levels of the biomarker. Such a test has not proved successful in several previous studies because CA125 can be elevated for a variety of reasons. Rather, the trial used several variables (dubbed the Risk of Ovarian Cancer Algorithm [ROCA]) that stratified women for ovarian cancer risk on the basis of their age and a comparison of their current CA125 results to previous levels. Those deemed at intermediate risk were stepped up to quarterly CA125 readings, whereas those deemed at high risk were given transvaginal sonography or ultrasound.

Over the 8 years, 85 (2.6%) of the women were referred for transvaginal sonography and a consultation or ultrasound. “The beauty of the ROCA algorithm is that every woman develops her own baseline,” Lu said.

He also said that the prospective, single-arm study did not yet support widespread use of the test. But he added that the preliminary results held out hope that the larger trial of the same method now under way in the UK would generate the mortality data needed to convince guideline writers that mass screening using personalized CA125 is a worthy early-detection tool.

Guidelines: No Test Works

The U.S. Preventive Services Task Force currently recommends against routine screening for ovarian cancer. The guidelines say, “there is no existing evidence that any screening test, including CA125, ultrasound, or pelvic examination, reduces mortality from ovarian cancer.”

The guidelines’ most recent update also noted that the existing tests, including the approach used in the UK trial, lead to anywhere from 3% to 12% of screened women being recalled for further testing and assessments, “resulting in potential distress and anxiety in otherwise healthy women.” It also pointed out that anywhere from 0.5% to 1% of those women “will suffer a significant complication because of surgery, based on published studies.”

A valid screening test has long been a goal of ovarian cancer researchers. Although the American Cancer Society estimated that cancer of the ovaries struck 21,500 women in 2009 (about 3% of all cancers in women), about 14,600 died from the disease, making it the fourth-leading lethal cancer among women. About 80% of ovarian cancers aren’t detected until their later stages, after they’ve invaded surrounding tissues and organs and can’t be fully removed with surgery. Chemotherapy regimens after surgery have a poor track record in these later stages.

Relying on symptoms to identify early-stage ovarian cancer has not proven successful, since serious pain doesn’t occur until the tumor is pressing on other organs. Symptoms such as early satiety, frequent urination, bloating, and pelvic pain are common to 90% of early-stage ovarian cancers, but those symptoms are not specific to ovarian cancer.

“The key for an ovarian cancer diagnostic test is not just to find the disease before a patient feels the symptoms; it’s to find the cancer while it’s still confined to the ovaries,” said Beth Karlan, M.D., director of the Women’s Cancer Research Institute at Cedars-Sinai Medical Center in Los Angeles. “Ovarian cancer has symptoms, but they are very nonspecific. We really do need to have a test that finds it at stage I.”

Although the personalized CA125 test that Lu and colleagues used has tantalized many leaders in the field, they worry about what wasn’t in the study’s abstract. One concern is the test’s sensitivity. “We don’t know whether lots more women in this group had early-stage ovarian cancer but didn’t have a change in CA125 levels,” said Robert Morgan, M.D., codirector of the gynecologic oncology program at City of Hope Cancer Center in Duarte, Calif., and chairman of the National Comprehensive Cancer Network’s ovarian cancer guidelines subcommittee. “That’s why it’s not ready for prime time.”

They also are concerned about the absence of data showing the improved mortality out-
comes that will be needed to justify use of the screening test in the general population. “Will it lead to a quantum improvement in overall survival?” asked Karlan. “Preventing advanced-stage disease is a far better way to go than coming up with treatments for advanced disease, but we have to be sober about this data because it’s a very small sample.”

Preliminary results from the larger UK study, published in *Lancet Oncology* in April 2009, were similar to Yu's findings. That trial, led by Ian Jacobs, M.D., at University College, London, randomly assigned more than 200,000 postmenopausal women aged between 50 and 74 years to either no screening (half the women) or one of two screening arms; the first used annual ultrasound testing alone and the other used a personalized CA125 test, based on the same algorithm, that had to show steadily rising levels before referral for ultrasound.

The arm that included personalized CA125 testing ultimately referred 97 (0.2%) women for surgery for suspected ovarian cancer. The arm that used annual ultrasound testing alone referred 845 women (1.8%) for surgery. The number of actual tumors detected was similar: 42 in the CA125 arm and 45 in the ultrasound arm.

But only some of those were early-stage invasive cancers. The overall positive predictive rate for invasive cancer was 35% in the CA125-before-ultrasound arm and 3% in the ultrasound arm. That is, when the personalized test was used as a prescreen, three operations were needed to identify one woman with ovarian cancer. With ultrasound alone, 30 operations were needed to find one cancer.

That finding is clearly superior to standards that clinicians in the field have established as a benchmark for a successful screening test. “For an ovarian cancer screening test to be rolled out, the minimum positive predictive value is 10%,” Karlan said. But even there, “you have to remove 10 ovaries to find one cancer.”

Even if the personalized CA125 test limits the number of false positives to acceptable levels and is eventually shown to improve mortality—the UK overall survival data are due in 2015—it won’t be a perfect test because of its lack of sensitivity. “At least 50% of patients with early-stage ovarian cancer were completely normal for CA125,” said City of Hope’s Morgan.

That outcome means that the search for a screening test will go on. And the process will include the quest for other biomarkers to add to CA125. “People think CA125 in combination with other biomarkers will be the best way to identify ovarian cancer early,” Morgan said. “There are probably 100 or 200 potential biomarkers in the medical literature for ovarian or other gynecological cancers. It creates a maze, but it’s our task to make it a straight line. It really is difficult.”

© Oxford University Press 2010. DOI: 10.1093/jnci/djq296