MedicalXpress

New screening strategy may catch ovarian cancer at early stages

August 26 2013

Evaluating its change over time, CA-125, the protein long-recognized for predicting ovarian cancer recurrence, now shows promise as a screening tool for early-stage disease, according to researchers at The University of Texas MD Anderson Cancer Center.

The updated findings are published in *Cancer*; preliminary data were first presented at the 2010 American Society of Clinical Oncology (ASCO) annual meeting. If a larger study shows survival benefit, the simple blood test could offer a much-needed screening tool to detect ovarian cancer in its early stages – even in the most aggressive forms – ¬in post-menopausal women at average risk for the disease.

MD Anderson has a long history in the research of the important biomarker. In the 1980s, Robert Bast, M.D., vice president for translational research at MD Anderson and co-investigator on the ASCO study, discovered CA-125 and its predictive value of ovarian cancer recurrence. Since then, researchers at MD Anderson and beyond have been trying to determine its role in early disease detection. The marker, however, can become elevated for reasons other than ovarian cancer, leading to false positives in early screening.

"Over the last ten years, there's been a lot of excitement over new markers and technologies in ovarian cancer," said Karen Lu, MD, professor and chair, Department of Gynecologic Oncology and the study's corresponding author. "I and other scientists in the gynecologic oncology community thought we would ultimately find a better marker

than CA-125 for the early detection of the disease. After looking at new markers and testing them head-to-head in strong, scientific studies, we found no marker better than CA-125."

According to the American Cancer Society, 22,240 women will be diagnosed with ovarian cancer in 2013 and another 14,030 are expected to die from the disease. The challenge, explained Lu, is that more than 70 percent of women with ovarian cancer are diagnosed with advanced disease.

"Finding a screening mechanism would be the Holy Grail in the fight against ovarian cancer, because when caught early it is not just treatable, but curable," said Lu, also the trial's principal investigator.

For the prospective, single-arm, 11-year study, 4,051 women were enrolled from seven sites across the country, with MD Anderson serving as the lead site. All were healthy, post-menopausal women, ages 50-74, with no strong family history of breast or ovarian cancer. The study's primary endpoint was specificity, or few false positives. In addition, the study looked at the positive predictive value, or the number of operations required to detect a case of ovarian cancer.

Each woman received a baseline CA-125 blood-test. Using the Risk of Ovarian Cancer Algorithm (ROCA), a mathematical model based on the patient's age and CA-125 score, women were stratified to one of three risks groups, with the respective follow-up: "low," came back in a year for a follow-up blood test; "intermediate," further monitoring with repeat CA-125 blood test in three months; and "high," referred to receive transvaginal sonography (TVS) and to see a gynecologic oncologist.

Based on the women's CA-125 change over time, the average annual rate of referral to the intermediate and high groups were 5.8 percent and .9

percent, respectively. Cumulatively, 85 women (2.9 percent) were determined to be high risk, and thereby received the TVS and were referred to a gynecologic oncologist. Of those women, 10 underwent surgery: four had invasive ovarian cancer; two had borderline disease; one had endometrial cancer and three had benign ovarian tumors – a positive predictive value of 40 percent, which greatly surpasses the clinical benchmark of 10 percent, say the researchers. The specificity of the test was 99.9 percent, explained Lu. The screening failed to detect two borderline ovarian cancers.

Of great importance, said Lu, is that the four invasive ovarian cancers detected were high-grade epithelial tumors, the most aggressive form of the disease, and were caught early (stage IC or IIB), when the disease is not only treatable, but most often curable. Lu also noted that all four women found to have invasive disease were monitored at low risk for three years or more prior to a rising CA-125.

"CA-125 is shed by only 80 percent of ovarian cancers," explained Bast, the study's senior author. "At present, we are planning a second trial that will evaluate a panel with four blood tests including CA-125 to detect the cancers we may otherwise miss with CA-125 alone. The current strategy is not perfect, but it appears to be a promising first step."

While encouraging, the findings are neither definitive, nor immediately practice-changing, stressed Lu; who also said a large, randomized prospective screening trial still needs to be conducted. Such research is ongoing in the United Kingdom; results from more than 200,000 women should be known by 2015.

"As a clinician treating women with this disease for more than ten years, I've become an admitted skeptic of ovarian cancer screening. Now, with these findings, I'm cautiously optimistic that in the not too distant future, we may be able to offer a screening method that can detect the disease in

its earliest, curable stages and make a difference in the lives of women with this now-devastating disease."

The study is continuing; and, as follow-up, Lu and her team plan to look at combining other markers with CA-125 to determine the screening impact of their combined change over time.

More information: "A 2-stage ovarian cancer screening strategy using the risk of ovarian cancer algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value." Karen H. Lu, Steven Skates, Mary A. Hernandez, Deepak Bedi, Therese Bevers, Leroy Leeds, Richard Moore, Cornelius Granai, Steven Harris, William Newland, Olasunkanmi Adeyinka, Jeremy Geffen, Michael T. Deavers, Charlotte C. Sun, Nora Horick, Herbert Fritsche, and Robert C. Bast. *CANCER*; Published Online: August 26, 2013 (DOI: 10.1002/cncr.28183).

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