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NOVEMBER/DECEMBER 2014

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The Power and Potential of HE4 in Ovarian Cancer

Despite advances over the years in understanding various aspects of ovarian cancer, the still quite lethal disease remains nearly impossible to detect in its beginning stages and difficult to determine when it starts to recur following treatment. **Kevin Holcomb, MD**, and **Jason D. Wright, MD,** direct the Gynecologic Oncology programs in the Departments of Obstetrics and Gynecology at NewYork-Presbyterian/Weill Cornell and NewYork-Presbyterian/Columbia, respectively. Drs. Holcomb and Wright have united their expertise in a concerted effort to confront these challenges. The target of their pursuit is human epididymis protein 4 or HE4 – a new potential biomarker that is known to be associated with ovarian cancer.

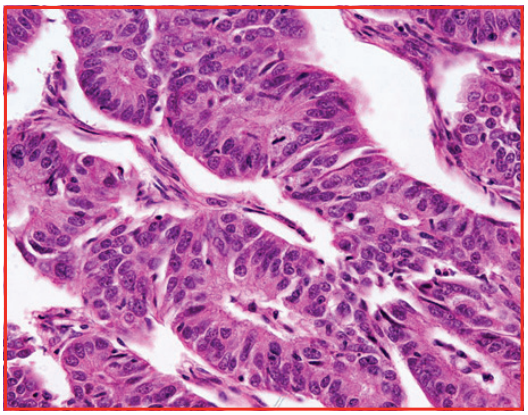
"HE4 is a biomarker that is measured in the bloodstream and that's secreted by a large number of ovarian cancers," says Dr. Wright. "We know many women with ovarian cancer will be positive for HE4. We're currently seeking to harness its potential as a screening for ovarian cancer or as a follow-up test to detect recurrences."

CA-125: The Current Gold Standard Test

"Those of us who care for women with ovarian cancer are fortunate to have another biomarker that we've used for many years – CA-125," says Dr. Holcomb. "This blood test has been proven effective in monitoring the response of patients with ovarian cancer to chemotherapy. Studies show that as CA-125 rises, it is usually associated with tumor progression; as CA-125 drops it's associated with a response."

The CA-125 test was developed in the early 1980s in the laboratory of **Robert C. Knapp, MD,** at Harvard Medical School. Dr. Knapp, who is now the William H. Baker Professor of Gynecology, Emeritus, at Harvard, is also a Visiting Scholar in Obstetrics and Gynecology at Weill Cornell Medical College. The article highlighting the work of Dr. Knapp and his colleagues on CA-125 was published in October 1983 in *The New England Journal of Medicine* and has since been cited more than 850 times – as recently as December 2014.

In a subsequent study, Dr. Knapp and his colleagues looked at a possible role for CA-125 in detecting recurrent ovarian cancer earlier than physical findings or symptoms in women in remission. The researchers obtained serum CA-125 levels from 55 women with epithelial ovarian cancer before a second-look surgical procedure and serially thereafter. All patients were clinically and radiographically free of tumor at the time of the second-look operation and were followed to clinical recurrence.



Ovarian adenocarcinoma at 20x magnification

CA-125 levels obtained at the second-look operation had a sensitivity and specificity for predicting clinical recurrence of 94 percent and 88 percent, respectively. Patients with an elevated CA-125 level greater than or equal to 35 U/ml had a 60 percent chance of clinical recurrence within four months, while patients with levels less than 35 U/ml had a 5 percent chance of clinical recurrence over the same time period. The CA-125 assay identified patients destined to suffer a clinical recurrence and provided a warning measurable in months. In fact, notes Dr. Holcomb, CA-125 is more sensitive than CT scans, with CA-125 levels elevating about four to five months earlier than when a CT scan can detect evidence of disease.

(continued on page 2)

The Power and Potential of HE4 in Ovarian Cancer

(continued from page 1)

"Dr. Knapp is famous for bringing CA-125 into practice, which, by far, is the most commonly used serum biomarker for ovarian cancer and the standard of care for evaluating a pelvic mass, monitoring a patient with ovarian cancer receiving chemotherapy, and determining recurrence after the completion of therapy," says Dr. Holcomb. "The test is a 'household name' for gynecological oncologists, and many women know of it as well. Dr. Knapp is now 85 years old and still involved in biomarker research. He continues to look for something better than what he brought to the market in the 1980s."

A few years ago, Dr. Knapp involved Dr. Holcomb in a research project looking at HE4 and comparing its effectiveness to CA-125 in a different setting. "We wanted to determine if this new blood test could predict the presence of cancer in women who have a mass on their ovary before they even have surgery," notes Dr. Holcomb. "We found that HE4 was more sensitive, but also much more specific for ovarian cancer and we could use the test to distinguish among benign, borderline, and malignant pelvic masses in premenopausal women presenting for surgery."

Dr. Kevin Holcomb

Drs. Holcomb, Knapp, and their research team conducted a subset analysis of data from a prospective clinical trial that enrolled women undergoing surgery for an adnexal mass.

Of 229 premenopausal patients, 195 (85 percent) had benign masses, 18 (8 percent) had epithelial ovarian cancer, and 16 (7 percent) had borderline ovarian tumor. The sensitivity of CA-125 and HE4 for detection of epithelial ovarian cancer was 83.3 percent and 88.9 percent, respectively. The specificity of CA-125 and HE4 was 59.5 percent and 91.8 percent, respectively.

Diagnostic Performance for EOC Detection

Variable	HE4	CA-125	HE4 and CA-125
Sensitivity	88.9%	83.3%	94.4%
Specificity	91.8%	59.5%	55.4%
PPV	50.0%	16.0%	16.3%
NPV	98.9%	97.5%	99.1%

EOC, epithelial ovarian cancer; ***HE4***, human epididymis protien 4; ***NPV***, negative predictive value; ***PPV***, positive predictive value

Source: Holcomb. HE4 for preoperative detection of EOC in premenopausal women with adnexal mass. *American Journal of Obstetrics and Gynecology 2011.*

A normal HE4 level ruled out invasive cancer in 98 percent of women with an elevated CA-125. "What the study demonstrated," says Dr. Holcomb, "is that premenopausal women presenting with an adnexal mass and elevation of both markers should be promptly referred to a gynecologic oncologist because the risk of an invasive cancer is significant and subspecialty care is associated with improved outcome."

As a result of this study and others like it, the National Health Service in the United Kingdom put forth a proposal to replace CA-125 with HE4 for all premenopausal women presenting with an adnexal mass.

"Serum biomarkers can be used in a number of different ways – to monitor chemotherapy response, to monitor patients who you are worried about having a recurrence, and to diagnose a mass that concerns you," says Dr. Holcomb. "So our first approach looked at HE4 tumor markers in women who had a mass on their ovary but didn't know if they had cancer preoperatively."

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>
> **— Dr. Kevin Holcomb**

With this information in hand, in women who already have a known ovarian cancer, might HE4 be a better monitoring test than the traditional marker CA-125? Dr. Holcomb and Dr. Wright hope that the solution will be found in two multi-center prospective trials following patients just before their surgery for ovarian cancer surgery and throughout their primary chemotherapy.

"Will HE4 supersede CA-125 as the gold standard test? Will it be complementary to CA-125? Will we be able to use these two biomarkers in combination in some fashion to better monitor patients? These are the major unanswered questions," says Dr. Wright. "What we are seeking to accomplish in these studies is to compare the performance of HE4 to CA-125."

"The first trial, which is now underway, is looking at HE4 compared to CA-125 for monitoring response to primary chemotherapy in patients with ovarian cancer," says Dr. Holcomb, who serves as principal investigator for both studies. "The second study will follow those patients after they complete primary

Dr. Jason D. Wright

therapy and when they go into remission, comparing CA-125 to HE4 in the detection of recurrence. If proven more effective in both the monitoring of primary response and for the detection of recurrence, HE4 could replace CA-125 as the standard of care in these situations."

In preparation for the two studies, an additional tube of blood is collected every time a CA-125 is drawn on a patient. "The HE4 level blood test will not be run right away," says Dr. Holcomb. "We're not using the HE4 in any way to clinically manage patients. After a predetermined number of patients have been treated, we're going to run all of the HE4s and compare the HE4 trend to the CA-125 trend to see if the HE4 test is more sensitive at predicting patients who would ultimately respond to chemotherapy, those who would progress, and those who would have stable disease."

The collaboration between the Divisions of Gynecologic Oncology at both sites of NewYork-Presbyterian on these studies is a natural. "We already have combined tumor boards and journal clubs, as well as a joint fellowship where fellows rotate between both campuses," says Dr. Wright. "These studies are an extension of our relationship. Patients can enroll at either Weill Cornell or Columbia."

With strength of the studies based in numbers of patients, the consortium of centers involved is growing, with trials opening at the University of Rochester Medical Center, Northwestern Memorial Hospital, and Montefiore Medical Center.

Earlier Detection of Recurrence and Survival Benefit

At this time, a survival advantage of early detection of ovarian cancer recurrence has not been established. "Some may question why then is a test that detects recurrence earlier than CA-125 needed," says Dr. Holcomb. "A recent study out of the United Kingdom looked at whether intervention in a recurrence setting made a difference in survival benefit. Unfortunately, in the end, there was no difference in overall survival. Women who underwent earlier interventions based on the CA-125 test did not live any longer than those who did not."

But Dr. Holcomb emphasizes that "it's not that we don't need newer tests that can achieve earlier diagnosis; it's that we need treatments in a recurrence that are more effective. While we currently have limited therapeutic options at the time of recurrence and little evidence that early intervention makes a difference in overall survival, that should not stop the search for more sensitive biomarkers. I'm hopeful for the day that we have more effective treatments in the recurrence setting where knowing quicker and earlier is going to make the difference between life and death."

Dr. Wright concurs. "There are a number of ongoing studies looking at new therapeutic treatments – whether those are chemotherapies or novel compounds that target specific pathways in ovarian cancer. One of the benefits of being treated at a place like NewYork-Presbyterian is that patients have access to the full spectrum of cutting-edge science and drug development."

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> **— Dr. Jason D. Wright**

In the meantime, adds Dr. Wright, "It is important for physicians to know that there are a lot of patients asking about screening tests for ovarian cancer and better ways to diagnose and monitor the disease. I believe there will be many advances coming down the pike of which HE4 is, potentially, one of those. Patients will have a unique opportunity to participate in trials like these, which can really advance the science of ovarian cancer. HE4 is certainly a biomarker that's very promising, and we are very fortunate here at NewYork-Presbyterian to be able to offer this test to our patients as part of these research studies."

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