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Doctors can unmask deceptive high-risk breast tumors using genetic profile

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A unique genetic signature can alert physicians to high-risk breast tumors that are masquerading as low-risk tumors, according to research at Washington University School of Medicine in St. Louis and collaborating institutions. Although these tumors are apparently estrogen-receptor positive — meaning they should depend on estrogen to grow — they don't respond well to anti-estrogen therapy.

Until now, doctors had no way to know these tumors would be unresponsive because their pathology is deceptive — the tumors appear to be more easily treatable estrogen-receptor-positive tumors, but they rapidly lose their estrogen receptors. The researchers demonstrated that the chance for cancer recurrence in such patients is significantly higher, and standard post-operative care with long-term anti-estrogen therapy is often not effective. The genetic signature defined by the researchers will permit doctors to identify their high-risk patients and direct them to more effective therapy.

"These tumors are like wolves in sheep's clothing," says Matthew Ellis, M.D., Ph.D., associate professor of medicine in the Division of Medical Oncology and a faculty member at the Siteman Cancer Center. "When these patients come in, their tumors test positive for estrogen receptors, so they are started on anti-estrogen treatment with the thought that they will do fine. But these tumors don't depend on estrogen at all for growth and will keep growing during the therapy. Now we have a robust way to identify such tumors soon after diagnosis."

The researchers findings will be presented June 2 at the 2008 American Society of Clinical Oncology Annual Meeting in Chicago.

"We've been interested in how to predict relapse in patients with estrogen-receptor-positive breast cancer," Ellis says. "So we looked for genetic expression profiles associated with relapse, but we took a very different approach from previous studies that addressed this question."

Instead of just profiling gene expression in patients' tumors at diagnosis, Ellis and colleagues at a number of other comprehensive cancer centers, also tested tumor gene expression one month after the start of treatment with letrozole, an aromatase inhibitor that blocks the body's estrogen production. All the study participants had been diagnosed with estrogen-receptor-positive tumors and were put on letrozole therapy to shrink tumors before surgery.

"It makes intuitive sense that the genetic features of the tumor in the presence of letrozole reflect the tumor's response to the drug and would be much more predictive of outcome than its features in the absence of the drug," explains Ellis, a Washington University oncologist at Barnes-Jewish Hospital.

The team first identified the 50-gene signature using pretreatment tumor samples. They compared gene expression in tumors of patients with estrogen-receptor-positive tumors who had good outcomes to those whose outcomes were poor.

Then they initiated a five-year clinical trial to assess the predictive ability of the gene expression profile when it was obtained after one month of letrozole therapy. In a study of 56 postmenopausal women with estrogen-receptor-positive stage 2 or 3 breast tumors, Ellis's group demonstrated that the post-letrozole genetic expression signature in the 50-gene set was much more predictive than the pretreatment genetic

profile. Based on the post-letrozole profile, they found they could rank tumors as low-, medium- and high-risk.

In the low-risk group, 81 percent of patients had a complete or partial response to treatment, which in addition to presurgical letrozole treatment included surgery followed by letrozole and radiation or chemotherapy at their doctors' discretion. In the medium-risk group, 70 percent had this favorable response; while in the high-risk group, only 25 percent responded to therapy.

Overall, 15 percent of study participants had high-risk estrogen-receptor-positive tumors that were shown to later switch to estrogen-receptor-negative tumors. Such tumors did not shrink during anti-estrogen treatment as do most estrogen-receptor-positive tumors, and patients with these tumors were far more likely to relapse. Two-thirds of high-risk patients experienced a relapse compared to 6 percent to 8 percent of the low- and medium-risk groups.

The research team plans to patent the gene-expression profile and make it available for use through University Genomics, a company co-owned by Washington University, the University of Utah and the University of North Carolina.

A clinical test for the high-risk gene expression signature is projected to be available for diagnostic use later this year and will be validated in clinical trials. Information about the test will be distributed at the ASCO meeting at the ARUP Laboratories (Associated Regional and University Pathologists Inc.) booth. ARUP is a national full-service reference laboratory owned by the University of Utah that will perform the gene-expression test.

Ellis says that it should be easy to incorporate the test into standard breast-cancer therapy protocols. As soon as patients are diagnosed with

estrogen-receptor-positive breast cancer, they would be placed on an anti-estrogen agent like letrozole. Then their tumors would be retested at the time of surgery to see if the gene-expression test indicates that their tumor has responded to the anti-estrogen agent.

"Those with resistant tumors would be shifted immediately following surgery to chemotherapy designed for patients with high-risk breast cancer," Ellis says. "That's extraordinarily powerful and a potentially big advance in individualized care."

Source: Washington University in St. Louis