Newly Identified Markers May Predict Who Will Respond to Breast Cancer Prevention Therapy

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Genetic variations, known as single nucleotide polymorphisms (SNPs), in or near the genes ZNF423 and CTSO were associated with breast cancer risk among women who underwent prevention therapy with tamoxifen and raloxifene, according to data published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

Women who have the favorable variations of these two SNPs are more likely to respond to prevention therapy, according to this study. Women who have the unfavorable variations of these SNPs may not benefit from prevention therapy, and they have a five-fold increased risk of developing breast cancer.

“The recent guidelines by the U.S. Preventive Services Task Force emphasize that selective estrogen receptor modulator (SERM) therapy with tamoxifen and raloxifene can lower a woman’s risk for developing breast cancer. But about 50 women have to be exposed to the treatment and side effects to prevent a single case of breast cancer,” said James N. Ingle, M.D., professor of oncology at the Mayo Clinic in Rochester, Minn.

“Our findings are important, because for the first time, we discovered genetic factors that could be used to select women who should be offered the drugs for prevention. Also of substantial importance is that we have discovered new information on how tamoxifen and raloxifene work to prevent breast cancer.”

Ingle and his colleagues at the Mayo Clinic, along with researchers at the National Surgical Adjuvant Breast and Bowel Project (NSABP) in Pittsburgh, Pa., and the RIKEN Center for Genomic Medicine in Tokyo, Japan, conducted a genome-wide association study involving 592 patients who developed breast cancer while on SERM therapy and 1,171 matched controls. They selected participants from the 33,000 women enrolled in the NSABP P-1 and P-2 breast cancer prevention trials.

He and his colleagues analyzed participants’ DNA using the Illumina Human610-Quad BeadChip to identify variations in their genetic makeup. They identified two SNPs that were most relevant to breast cancer risk, one in the gene ZNF423, and the other near the gene CTSO.

“Our discovery is a major step toward truly individualized prevention of breast cancer. Findings from our study provide clear direction as to which women are likely and which are unlikely to benefit from tamoxifen or raloxifene,” said Ingle. “The best chance we have of decreasing the burden of breast cancer is to prevent it in the first place. Our findings provide the basis for a reinvigoration of research efforts in breast cancer prevention.”

The researchers conducted further experiments using breast cancer cell lines harboring either the most common variation or the less common variation of the SNPs. They found that in cells with the most common variation of the SNPs, estrogen increased expression of both ZNF423 and CTSO, as well as expression of BRCA1, a gene related to breast cancer risk. Estrogen did not increase expression of these genes in cells that had the less common form of the SNPs.

When tamoxifen or raloxifene were added to estrogen, there was a striking reversal in the patterns of expression of ZNF423 and BRCA1. In cells with the less common ZNF423 SNP, expression of ZNF423 and BRCA1 rose dramatically. This reversal in expression patterns provides a potential explanation for the decreased occurrence of breast cancer in women undergoing SERM therapy who carry this SNP.

In addition, the researchers found that the different forms of the ZNF423 and CTSO SNPs predicted the odds for developing breast cancer while undergoing SERM therapy: Women who had the favorable variations of both the SNPs had the lowest risk and women who had the unfavorable variations of both the SNPs had a more than five-fold relative increased risk for developing breast cancer.

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