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News Bureau
200 First Street SW
Rochester, Minnesota 55905
http://www.mayoclinic.org

Contact:

Joe Dangor
507-284-5005 (days)
507-284-2511 (evenings)
Email: newsbureau@mayo.edu

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Cancer Discovery

Genetic Variations May Help Identify Best Candidates for Preventive Breast Cancer Drugs

ROCHESTER, Minn. — Newly discovered genetic variations may help predict breast cancer risk in women who receive preventive breast cancer therapy with the selective estrogen receptor modulator drugs tamoxifen and raloxifene, a Mayo Clinic-led study has found. The study is published in journal *Cancer Discovery*.

"Our findings are important, because we identified genetic factors that could eventually be used to select women who should be offered the drugs for prevention," said James Ingle, M.D., an oncologist at Mayo Clinic.

Dr. Ingle and collaborators at the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the RIKEN Center for Genomic Medicine conducted a genome-wide association study involving 592 patients who developed breast cancer while receiving preventive therapy and 1,171 matched controls. Participants were selected from 33,000 women enrolled in the NSABP breast cancer prevention trials. This research was supported by a Pharmacogenomics Research Network grant from the National Institute of General Medical Science and the National Cancer Institute.

The researchers analyzed participants' DNA to identify variations in their genetic makeup and identified genetic two variations, or single nucleotide polymorphisms (SNPs), that were associated with breast cancer risk in or near the genes ZNF423 and CTSO.

They discovered that women with favorable variations in these genes were more likely to respond to preventive therapy with the drugs while women with unfavorable variations may not. In addition, women with unfavorable variations had a five-fold increased risk of developing breast cancer.

Dr. Ingle says the recent guidelines by the U.S. Preventive Services Task Force emphasize that selective estrogen receptor modulators (SERM) therapy with tamoxifen and raloxifene can lower a woman's risk for developing breast cancer. However, there currently is no way to know which women will benefit from the therapy.

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"This is a major step toward truly individualized prevention of breast cancer," says Dr. Ingle. "Our findings provide clear direction as to which women are likely and which are unlikely to benefit from tamoxifen or raloxifene." Dr. Ingle says the findings provide the basis for a reinvigoration of research efforts in breast cancer prevention.

The researchers also studied breast cancer cell lines with the most common variation and 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, and the expression of BRCA1, a gene associated with breast cancer risk. Estrogen did not increase expression of these genes in cells that had the less common form of the SNPs. Importantly, however, 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.

About Mayo Clinic Cancer Center

As a leading institution funded by the National Cancer Institute, Mayo Clinic Cancer Center conducts basic, clinical and population science research, translating discoveries into improved methods for prevention, diagnosis, prognosis and therapy. For information on cancer clinical trials, call **507-538-7623**

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