

IN THE SPOTLIGHT

Scanning for Clues to Better Use Selective Estrogen Receptor Modulators

Mitchell J. Machiela and Stephen J. Chanock

Summary: Ingle and colleagues present timely findings identifying genetic variants associated with response to selective estrogen receptor modulator therapy that when substantiated in follow-up may represent an important step toward understanding estrogen-dependent induction of *BRCA1* expression and advancing individualized preventive medicine in women at high risk for developing breast cancer. *Cancer Discov*; 3(7): 728-9. ©2013 AACR.

See related article by Ingle et al., p. 812 (1).

In this issue of *Cancer Discovery*, Ingle and colleagues (1) report a set of genetic variants in the *ZNF423* gene on chromosome 16q12 that is associated with response to selective estrogen receptor modulator (SERM) therapy, an approved prevention therapy for breast cancer (2). The genetic markers were identified in a genome-wide association study (GWAS) of participants in the National Surgical Adjuvant Breast and Bowel Project P-1 and P-2 breast cancer prevention trials. The authors pursued functional studies of the plausible candidate genes in this region and have singled out risk alleles that influence estrogen-dependent induction of *BRCA1* expression.

The public health impact of effective prevention therapy for breast cancer could be substantial. Worldwide, breast cancer is the cancer with the highest incidence in women and remains the most common cause of cancer-related death among women (3). Globally, an estimated 1.38 million new cases are diagnosed each year, and its incidence is expected to rise, particularly in the developing world, as life expectancy increases (4). A subset of women with family history, particularly those harboring *BRCA1* or *BRCA2* mutations, is at an increased risk of developing breast cancer relative to the general population. For these women, intensive effort has focused on targeted therapies as well as strategies, such as SERMs, to prevent breast cancer in the high-risk setting.

SERMs are pharmacologic agents that compete with estrogen for binding to the estrogen receptor and have pleiotropic effects, some agonistic and others antagonistic. Despite the 'proven' use of U.S. Food and Drug Administration-approved SERM therapy, namely, tamoxifen and raloxifene, these drugs have not been widely prescribed, partly due to the rare but serious adverse side effects of deep vein thrombosis with pulmonary embolisms and increased risk of endometrial cancer. Moreover, the number of women treated to prevent a case of breast cancer in the general population is high; it is estimated

that approximately 50 women need to receive a 5-year course of SERM therapy to prevent a single case of breast cancer (5). Designing a tailored approach to SERM therapy that targets women most likely to benefit from the therapy may result in a more favorable risk-to-benefit ratio, which, in turn, may lead to wider usage.

Ingle and colleagues (1) set out to identify common genetic markers that could be used in discriminating risk for women receiving SERM. An initial discovery GWAS was wisely conducted in a nested case-control study from SERM breast cancer prevention trials. It yielded promising regions on chromosomes 4q32, 13q12, and 16q12, but each failed to reach genome-wide significance, a threshold that protects against false positives. This is especially important because follow-up mapping and functional studies are costly, in terms of both expense and effort (6). To their credit, they took a small risk based on the promising genetic signal in the GWAS and proceeded to investigate the biology of the plausible candidate genes *ZNF423* and *CTSO* on chromosomes 16 and 4, respectively; single-nucleotide polymorphisms (SNP) on chromosome 16 protected against breast cancer, whereas those on chromosome 4 increased risk.

The authors used a panel of 300 well-characterized lymphoblastoid cell lines as a model system to map genetic variants with regulatory elements (7, 8). While some may quibble with the fact that the studies were not conducted in breast cancer cell lines, the use of this model system was instrumental in characterizing functional elements that mapped to common variants in *ZNF423* and *CTSO*, both of which are estrogen-dependent and regulate *BRCA1* expression. Further studies in breast cancer cell lines and tissues will be needed to further elucidate the pathway as well as the differences attributable to the risk variants. Still, the SNP array and mRNA expression data from the lymphoblastoid cell line panel can readily complement experiments from other cell lines to provide additional functional evidence for an array of clinical and pharmacogenomics hypotheses.

Wild-type *ZNF423* expression increased with higher estrogen levels and, in turn, acts as a transcription factor for *BRCA1* and *BRCA1*-induced DNA double-strand break repair. Functional analyses indicated that SNP rs9940645 in *ZNF423* caused differential estrogen receptor alpha binding to a nearby estrogen response element. Greater binding was

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present for the wild-type genotype in the presence of estrogen alone, and a reversal of the binding pattern was observed in the presence of estrogen and an active metabolite of tamoxifen. This intriguing example of investigating the biologic underpinnings of an association resulted in the observation that the decrease in risk associated with rs9940645 could work through tamoxifen or raloxifene because of a more robust estrogen-dependent induction of *ZNF423* with the protective variant.

Further work is needed to fully explain the allele-specific effects of the SNP rs9940645 in the *ZNF423* gene with respect to SERM therapy and breast cancer risk. Substantial effort, however, is necessary to translate such an experimental finding into clinical practice. Studies still need to assess whether significantly different breast cancer risks exist between women carrying the rs9940645 variant on SERM therapy and women carrying the rs9940645 variant not on SERM therapy. Studies also need to address whether the number of women who need to be treated to prevent one case of breast cancer decreases if only women carrying the *ZNF423* variant are administered a 5-year course of SERM therapy.

In summary, this study provides several new clues that could advance the field of breast cancer prevention. First, it points to a genetic region on chromosome 16q12 that harbors common alleles that influence breast cancer risk during SERM therapy. Second, the functional pursuit of promising genetic markers has led to the characterization of *ZNF423* as an estrogen-inducible BRCA1 transcription factor. In turn, this new biologic insight sheds light on both the genetic association as well as a new pathway for development of therapeutic or preventive strategies. If the results of this study are substantiated in follow-up, a woman's genotype could be useful in assessing when and if to use SERMs. In this regard, it could lead to improved acceptance of SERM therapy, thus restricting preventive SERM therapy to a subset of high-risk women and thereby administering SERMs to fewer women per prevented case of breast cancer. In parallel, it will be critical to pursue studies to uncover genes, through either GWAS or targeted studies, that identify both

markers and the basis for the concerning side effects of SERM, deep vein thrombosis with pulmonary embolus and endometrial cancer (5). In conclusion, this study represents a small, but real step toward developing tailored therapies to prevent breast cancer, particularly in high-risk women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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