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Scanning for Clues to Better Use Selective Estrogen Receptor Modulators

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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 towards understanding estrogen-dependent induction of BRCA1 expression and advancing individualized preventive medicine in women at high risk for developing breast cancer.

In this issue of *Cancer Discovery*, Ingle and colleagues report a set of genetic variants in the *ZNF423* gene on chromosome 16q12 that are associated with response to selective estrogen receptor modulator (SERM) therapy, an approved prevention therapy for breast cancer (1). The genetic markers were identified in a genome-wide association study (GWAS) of participants in the NSABP 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 has the highest incidence in women and remains the most common cause of cancer-related death among women (2). 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 (3). A subset of women with family history, particularly those harboring *BRCA1* or *BRCA2* mutations, are 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 preventive strategies, such as SERM, 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’ utility of FDA-approved SERM therapy, namely, tamoxifen and raloxifene, they 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

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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 (4). 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 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 chromosome 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 cost and effort (5). 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 (SNPs) on chromosome 16 protected against breast cancer while 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 (6, 7). While some may quibble with the fact that the studies were not conducted in breast 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 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 biological 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 if 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 needed to

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treat to prevent one case of breast cancer decreases if only women carrying *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. 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 biological 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 SERM. In this regard, it could lead to improving acceptance of SERM therapy and thus, restrict preventive SERM to a subset of high-risk women and thereby administer SERM to fewer women per prevented case of breast cancer. In parallel, it will be critical to pursue studies to uncover genes, either through 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 (4). In conclusion, this study represents a small, but real step towards developing tailored therapies to prevent breast cancer, particularly in high-risk women.

References

1. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Journal of the National Cancer Institute. 1998; 90:1371–88. [PubMed: 9747868]
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer Journal international du cancer. 2010; 127:2893–917. [PubMed: 21351269]
3. Thun MJ, DeLancey JO, Center MM, Jemal A, Ward EM. The global burden of cancer: priorities for prevention. Carcinogenesis. 2010; 31:100–10. [PubMed: 19934210]
4. Santen RJ, Boyd NF, Chlebowski RT, Cummings S, Cuzick J, Dowsett M, et al. Critical assessment of new risk factors for breast cancer: considerations for development of an improved risk prediction model. Endocrine-related cancer. 2007; 14:169–87. [PubMed: 17639036]
5. Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, et al. Replicating genotype-phenotype associations. Nature. 2007; 447:655–60. [PubMed: 17554299]
6. Ingle JN, Schaid DJ, Goss PE, Liu M, Mushiroda T, Chapman JA, et al. Genome-wide associations and functional genomic studies of musculoskeletal adverse events in women receiving aromatase inhibitors. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2010; 28:4674–82. [PubMed: 20876420]
7. Liu M, Wang L, Bongartz T, Hawse JR, Markovic SN, Schaid DJ, et al. Aromatase inhibitors, estrogens and musculoskeletal pain: estrogen-dependent T-cell leukemia 1A (TCL1A) gene-mediated regulation of cytokine expression. Breast cancer research: BCR. 2012; 14:R41. [PubMed: 22405131]