

## Unraveling Genes, Hormones, and Breast Cancer

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Findings reported by Johnson et al. (1) in this issue of the Journal exemplify the value of using quantitative measures of hormone exposure and combining large studies to identify breast cancer genetic susceptibility loci involved in hormonal carcinogenesis. Accumulating data from investigations of other cancer sites are starting to interrelate genetic and environmental factors to risk (2,3), but, to date, there has been limited success in identifying such relationships for breast cancer. Given that breast cancer is well known to be influenced by a variety of hormonally related risk factors (4), it is of note that this study focused on the interplay of genetics and endogenous hormones.

As discussed by Johnson et al. (1), a number of studies have identified some key endogenous hormones associated with the risk of postmenopausal breast cancer (5), but few studies have successfully linked these hormones to the risk of premenopausal cancer. The failure to fully understand the role of endogenous hormones in breast cancer etiology is undoubtedly due to difficulties in reliably measuring hormones, which are complex in both their metabolic pathways and interactions with other biological markers. In addition, for premenopausal women, the wide variation in hormone levels over the menstrual cycle requires careful attention to the timing of sample collections.

Using a novel approach for measuring estrone glucuronide (E1G) (6) that accounts for cyclic variation in hormone levels during the periovulatory and luteal phases of the menstrual cycle, Johnson et al. (1) observed that lower urinary E1G levels were associated with a single-nucleotide polymorphism (SNP) in the cytochrome P450 3A gene (*CYP3A*). Furthermore, using data from targeted genotyping and genome-wide association study (GWAS) datasets comprising more than 10 000 breast cancers and 17 000 control subjects, they found that a proxy SNP that tags the *CYP3A* SNP was associated with a weak reduction in the risk of breast cancer.

It is noteworthy that the *CYP3A* SNP was associated with the risk of breast cancer only for a select subgroup of women, notably those younger than 50 years. This finding could reflect an enhanced ability to detect gene–hormone interactions among women with higher estrogen levels. It could also reflect that breast cancers among younger women tend to have distinct risk factors and molecular characteristics that distinguish them from the more commonly occurring postmenopausal breast cancers. Notable differences in risk for breast cancer among younger vs older women include enhanced effects of family histories of breast cancer, an inverse (rather than positive) association with obesity, and possibly increased (rather than decreased) risks with parity, presumably reflecting a transient increase in risk following childbirth (7).

Furthermore, the observation that the *CYP3A* SNP was associated with the risk of breast cancer among younger women (1) is in line with the recognition that breast cancers are heterogeneous with respect to incidence, clinical behavior, morphological appearance, and molecular profiles. Efforts of various consortia are identifying subtype-specific genetic susceptibility loci, as it has become clear that genetic markers can have unique relationships according to important clinical features of breast cancer, such as estrogen receptor, progesterone receptor, human epidermal growth factor receptor, tumor grade, and histology (8–10). Younger women are of particular interest given their predisposition to developing estrogen receptor–negative, triple-negative, and basal-like breast cancers (11). The associations with receptor-negative and basal-like breast cancers are particularly strong when examined in certain racial subgroups, such as African and African American women (12).

A potential limitation of the study was that the *CYP3A* SNP that was associated with E1G levels and breast cancer risk was identified through a candidate gene approach rather than GWAS approaches. Had agnostic GWAS approaches been used to detect SNPs associated with E1G levels, other relevant genetic risk predictors might have been identified. GWAS studies are also identifying loci associated with breast cancer subtypes in diverse populations (13–15), and the findings by Johnson et al. (1) suggest that future GWAS efforts in concert with more refined phenotype measures could expand our understanding of hormonal exposures related to breast carcinogenesis.

The appropriate methods to reliably measure hormones in premenopausal women and the key biochemical isoforms relevant to breast cancer risk remain unclear. Although the E1G measurement used in the study is novel, it is not without interpretative difficulties due to issues in measurement reproducibility and its unknown relationship(s) with hormone markers used in other studies. Johnson et al. (1) evaluated only one isoform of excreted estrogen—E1G—and it is unclear how this E1G marker relates to other hormone measurements that have been examined in relation to the risk of breast cancer. Although radioimmunoassays have been most commonly used to measure estrogens, other sensitive methods are being evaluated, including a liquid chromatography–mass spectrometry technique that simultaneously measures 15 estrogen metabolites (16). In fact, a recent report from the Nurses' Health Study that used this assay found that women with higher urinary excretion of parent estrogens had a reduced risk of breast cancer (17). Future studies will need to reconcile these apparently discrepant findings, as well as attempt to understand interrelationships of endogenous hormones with other circulating markers associated with breast cancer risk, including androgens, prolactin,

and insulinlike growth factors (18–20). Furthermore, because it is thought that the cumulative lifetime exposure to hormones is one of the drivers of an increased risk of breast cancer (21), a limitation for many studies is that they capture only one moment in time. Accordingly, biomarkers that could reflect the cumulative effects of hormone exposure at the level of breast tissue and over the course of a woman's life (ie, at critical times of susceptibility) could be used to identify additional breast cancer susceptibility loci.

It is clear that we are only beginning to understand how genetic factors influence hormones and, in turn, how these factors interact to influence breast cancer risk. The findings by Johnson et al. and others emphasize the complexities involved in enhancing our understanding of these relationships but also provide encouragement for future efforts to expand our knowledge. Improved capacities for identifying genetic, hormonal, and other relevant exposure markers, combined with consortial approaches to provide the necessary statistical power to examine interactions, should provide powerful tools for future insights.

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