Adding Common Genetic Variants to Breast Cancer Risk Models Offers Only Small Benefit

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(PhysOrg.com) -- Scientists report that breast cancer risk assessment models, which predict a woman's chance of developing breast cancer, do not perform better when they include common inherited genetic variants recently linked to the disease. Therefore, recommendations for breast cancer screening or treatments will remain unchanged for most women. The study, led by investigators from the National Cancer Institute (NCI), part of the National Institutes of Health, appears in the March 18, 2010, *New England Journal of Medicine*.

"In the past three years, genome-wide association studies have identified multiple common genetic variants associated with breast cancer. The extent to which adding these variants to existing models could improve clinical recommendations had not been tested in a large population of women prior to this study," said Sholom Wacholder, Ph.D., senior investigator in NCI's Division of Cancer Epidemiology and Genetics (DCEG). "When we included these newly discovered genetic factors, we found some improvement in the performance of risk models for breast cancer, but it was not enough improvement to matter for the great majority of women."

Findings from genome-wide association studies (GWAS) to date have pinpointed several locations in the human genome, called single-nucleotide polymorphisms (SNPs), where genetic variation is associated with cancer risk. SNPs are the most common type of variation, affecting just a single building block of DNA. SNPs are used in GWAS to identify chromosome regions that are associated with disease. Studies to characterize the biologic effects of the variants associated with breast cancer are now being conducted to help clarify their role in breast cancer risk.

To test whether genetic information from recent genome-wide association studies would increase the value of breast cancer risk models, Wacholder and colleagues combined data from five studies: the Nurses' Health Study; the Womens' Health Initiative Observational Study; the American Cancer Society Cancer Prevention Study II Nutrition Cohort; the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and the Polish Breast Cancer Study, in order to provide more reliable and accurate estimates than those available from any single study. These studies, altogether, included 5,590 breast cancer patients and 5,998 women without cancer. The women were predominately white and between the ages of 50 and 79. The team assembled information for each participant on established risk factors and on the 10 SNPs recently found to be associated with breast cancer risk in analyses of GWAS.

Next, the investigators examined the predictive accuracy of the Gail model"the most commonly used breast cancer risk model"for this group of women. The Gail model uses information on a woman's own personal medical and reproductive history, as well as the history of breast cancer among her first-degree relatives (mother, sisters, and children) to estimate her risk of developing invasive breast cancer within the next five years, or over her lifetime. The investigators then tested the accuracy of a SNP model and found that it was as good as the Gail model alone. An inclusive model, using both SNPs and Gail factors, performed only slightly better than either model alone.

For most women in the study, the inclusive model did not substantially change their personal estimated risk of developing breast cancer beyond the Gail model calculations. Overall, using the inclusive model reclassified 26 percent of women to a higher risk category; 28 percent to a lower risk

category; and left 46 percent in the same category of risk score. The shifts from one category to another were generally too small to influence clinical decision-making.

The authors emphasized that the genome-wide association studies represent an early stage in our understanding of the inherited components of breast cancer risk. "We can expect to identify more genetic determinants of breast cancer, and to learn more about those we have already found," said Wacholder. "This information, along with our increasing knowledge of non-genetic factors, should allow us to steadily improve our risk prediction models for breast cancer."

More information: Wacholder S, et al., Adding Common Genetic Variants to Breast Cancer Risk Models. The New England Journal of Medicine, Mar. 18, 2010. DOI:10.1056/NEJMoa0907727

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