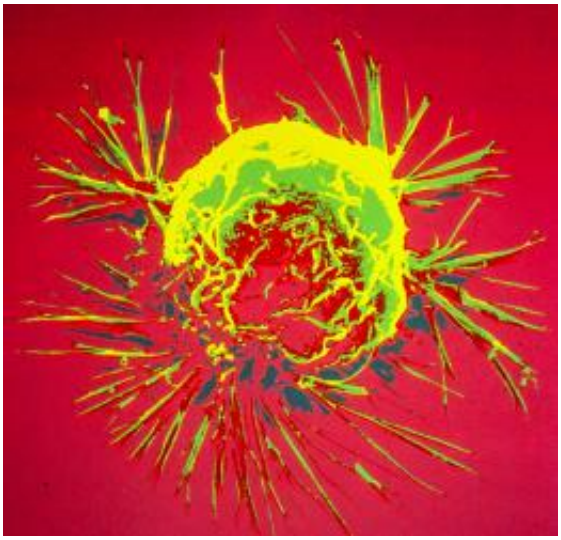
MedicalXpress

Newly identified genetic variants found to increase breast cancer risk

March 30 2009



A breast cancer cell photographed by a scanning electron microscope, which produces 3-dimensional images. This image shows the overall shape of the cell's surface at a very high magnification. Image: National Cancer Institute

(PhysOrg.com) -- A large-scale effort to identify genetic markers of breast cancer has uncovered two common genetic variants that increase risk of the disease in women of European ancestry.

The paper, published in advance online in Nature Genetics on March 29, is part of an ongoing effort led by a team of researchers from the Harvard School of Public Health (HSPH), Brigham and Women's Hospital (BWH), the U.S. National Cancer Institute (NCI), and other

collaborators. In a different paper published in the same issue, another consortium of scientists led by a U.K.-based group announces the discovery of additional variants that are significantly associated with a predisposition for breast cancer.

"By discovering these variants, we hope to understand more about the biology of breast cancer," says David Hunter, a professor in cancer prevention at HSPH who is senior author of the U.S. study and a co-author of the U.K.-led study. The current findings add to variants previously identified in similar studies in 2007.

Scientists believe there could be many additional genetic variants associated with breast cancer still lurking in the genome. They hope that uncovering these variants will help them understand the underlying causes of breast cancer and develop therapies. In addition, scientists suggest that the information could be used in the future as a risk prediction tool that would help tailor cancer prevention efforts to individual women. The current findings "add to a growing list of variants that could eventually be used to identify women who are at higher or lower risk," Hunter says.

Combination of common genetic factors can confer risk

A woman is more likely to develop breast cancer if she has a family history of the disease, suggesting that it can be partly explained by inherited genetic factors. A small percentage of women carry rare genetic mutations that give them a much higher risk of breast cancer, but the majority of the inherited risk of breast cancer is thought to stem from a combination of common genetic factors, each conferring a small amount of risk.

Genome-wide association studies such as the one described in Nature Genetics analyze genetic variants across the genome in large numbers of DNA samples to identify these weaker but more common variants. The discovery of new genetic variants relies on collaborative efforts to pool large data sets from many studies; the analyses are conducted in multiple stages in order to find true associations among false-positives.

In this study, the scientists first analyzed more than 500,000 gene variants, or single nucleotide polymorphisms (SNPs), using blood samples taken from 1,145 postmenopausal women in the Nurses' Health Study cohort based at BWH who had developed invasive breast cancer.

These variants were compared to samples from 1,142 women who had not developed the disease, revealing candidates for a possible association with breast cancer. In a second stage of the study, the researchers took nearly 25,000 of the top-candidate variants and analyzed them in an additional 4,547 cases and 4,434 controls from four studies. In the third stage, the top 21 of the resulting candidates were analyzed in an additional 4,078 cases and 5,223 controls.

After this three-part analysis, the researchers found two previously unidentified genetic variants that were significantly associated with breast cancer. The first variant is located on a region of chromosome 1 with an unknown function. The second variant is located within a gene on chromosome 14 that is involved in DNA repair, called RAD51L1. Hunter says that defects in DNA repair are known to underlie some rare familiar forms of breast cancer, but that "this is the first time that a common variant in a gene involved in DNA repair has been associated with breast cancer."

Hunter says that it's almost certain that more variants will be found because the common variants that have been linked to breast cancer to date do not account for the total amount of inherited risk of the disease.

But he says that with technologies and collaborations in place to conduct genome-wide association studies, finding further variants is only a matter of continuing these efforts. "The good news is that we now have the capacity to move this forward in a very logical and stepwise manner," he says. "It really is just a matter of applying the new technologies to larger numbers of cases."

Peter Kraft, associate professor of epidemiology at HSPH and a co-author of the paper, says that as more and more variants emerge, it may be possible to use them as a tool to predict an individual's risk of developing breast cancer. Kraft says that it's still unclear whether genetic variations discovered by these studies will ever contribute enough risk to guide drastic or invasive prevention strategies, such as prophylactic mastectomy.

But he says that this genetic information, if used in combination with family history and lifestyle factors, could help physicians identify women who should undergo more aggressive screening or counseling to prevent and detect breast cancer.

This study was conducted under the auspices of the Cancer Genetic Markers of Susceptibility (CGEMS) initiative of the NCI co-directed by Hunter, Stephen Chanock, Robert Hoover, and Gilles Thomas of the NCI.

Provided by Harvard University (news : web)