looking for more-accurate ways to predict which women are at highest risk of developing breast cancer.

Cancer geneticist Kenneth Offit

Now, an international team led by Memorial Sloan Kettering cancer geneticist Kenneth Offit has identified additional genetic variations that change a woman's risk. This information will allow investigators to create a model to more accurately predict the breast cancer risk of an individual woman.

The model will be specific to women with mutations in the gene *BRCA2,* although it may be extended to include *BRCA1* as well. In 1996, Dr. Offit's laboratory identified the most common mutation of *BRCA2,* which they have also linked to hereditary cases o ovarian, prostate, and pancreatic cancers.

"Currently, when a woman learns she has a *BRCA2* mutation, we tell her that her risk of developing breast cancer in her lifetime is between 40 and 80 percent," Dr. Offit says. "Because this is a large range, women face the difficult decision of choosing between undergoing preventive surgery or having regular surveillance with MRIs and mammograms. Being able to more accurately predict that risk is of great relevance to them."

Focus on Genetic Variations

Dr. Offit's latest paper, which was published March 27 in the journal *PLoS Genetics*, is part of a larger group of studies being released this week that report on dozens of genetic variations that affect the risk of breast, prostate, and ovarian cancers. These genetic variations, called single nucleotide polymorphisms (SNPs, pronounced "snips"), involve changes in only one of the four nucleotide bases — T, C, G, or A — of the DNA code.

"Individually, these kinds of variations are very weak risk markers for people in the general population who have an average risk of developing cancer," Dr. Offit says. "However, for women who are known to be at greatly elevated risk because of a mutation in a gene such as *BRCA2*, these SNPs — especially when combined with each other — can help us greatly refine our predictions and provide women with more information."

To pinpoint common genetic variations that modify the breast cancer risk associated with *BRCA2*, Dr. Offit's team studied 211,155 genetic variants in 3,881 women who had breast cancer and 4,330 women who did not. All the women were drawn from a database of *BRCA2* mutation carriers.

This particular study identified a new SNP found on chromosome 6 that was associated with a slightly lower risk of breast cancer. Some other SNPs previously discovered by the investigators are associated with a higher risk.

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Building a More Accurate Prediction Model

Based on the latest SNP identified, as well as 13 others, Dr. Offit's team has developed a new prediction model, which he will begin evaluating soon as part of a clinical trial.

"Instead of telling women their risk of developing breast cancer is between 40 and 80 percent, we should be able to tell them whether they are on the high end of that range or the low end. We may eventually be able to provide a more specific number," he says.

"The scientific aim of the trial will be to validate the accuracy of the model, but we are also really interested in the translational part of this model," Dr. Offit adds. "We want to learn how women will use this additional information. We've recruited a behavioral psychologist to help us study how women will factor our new risk number into their decision-making process."

Many factors beyond numbers influence how an individual woman responds to a *BRCA2* diagnosis, including family history and her personality traits.

Dr. Offit also emphasizes the importance of collaboration on this kind of international, multicenter trial. "It's amazing to have researchers around the world who are working on this, and it shows real unity in genetic research," he says. "It demonstrates the role that Memorial Sloan Kettering can play in leading one of these studies. Major grants from the Starr Foundation and the Breast Cancer Research Foundation have allowed us to carry this work forward."

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