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Genetic tests help identify relative risk of 25 cancer-associated mutations

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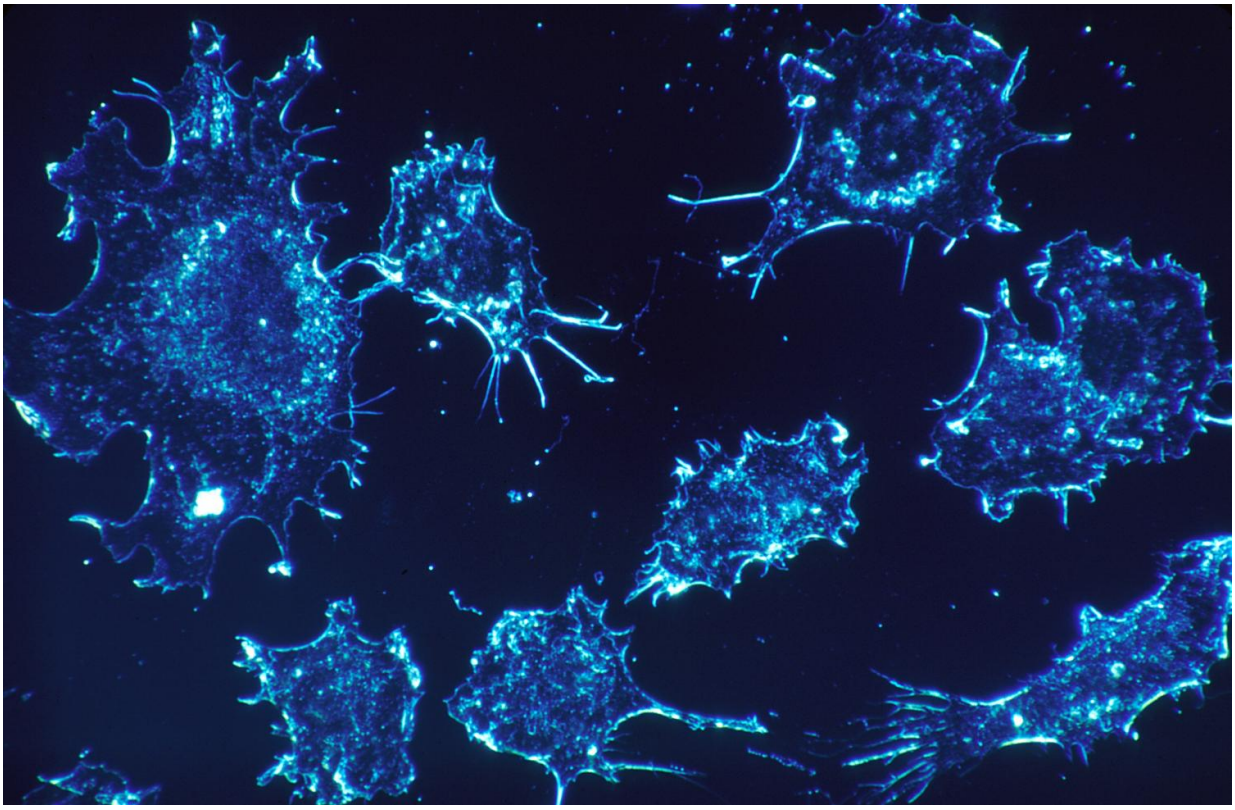

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No one wants to hear that they have a mutation in their DNA associated with the development of cancer. But it may be even more difficult to accept that, in many cases, clinicians can't say whether or by how much that mutation might increase a person's actual risk of developing the

disease. This uncertainty causes anxiety and clouds treatment decisions.

Now, in the largest study of its kind, researchers at the Stanford University School of Medicine and Fox Chase Cancer Center in Philadelphia have analyzed the genetic test results, family histories and disease status of nearly 95,600 women who underwent genetic testing for 25 mutations associated with the development of breast and ovarian cancer. Some of the women had cancer; many did not. Seven percent of the women in the study carried at least one of the mutations, the researchers found.

The researchers hope the study is the first step to providing much-needed clarity to women and their physicians as they struggle to interpret the results of genetic testing. It may also help guideline-making organizations such as the American Cancer Society recommend when additional or more-frequent screening tests might be appropriate.

"The results of this study will help to personalize our risk estimates and recommendations for preventive care," said Allison Kurian, MD, associate professor of medicine and of health research and policy at Stanford. "A better understanding of cancer risks can help women and their clinicians make better-informed decision about options to manage cancer risk."

For example, Kurian said, some women with a high risk of developing breast cancer might consider preventive mastectomy, whereas those with lower risk—for example, a twofold elevation over the average risk—might instead pursue intensive regular screening, including breast magnetic resonance imaging.

Kurian is the lead author of the study, which will be published online June 27 in *JCO Precision Oncology*. Michael Hall, MD, associate professor of clinical genetics at the Fox Chase Cancer Center, is the

senior author. The study was funded by Salt Lake City-based Myriad Genetics Inc., which performed the genetic testing.

What does a mutation mean?

Increasingly, women who are tested for a panel of cancer-associated mutations are given a mixed bag of results. Advances in DNA sequencing have made it quicker, easier and cheaper to identify mutations in an ever-growing panel of cancer-associated genes. With the exception of a few well-studied mutations such as BRCA1 and BRCA2, however, the exact effect of most of these remains murky because few large-scale studies have been completed.

The researchers assessed the mutation status of 95,561 women with and without the disease who chose to have their genome tested by Myriad Genetics for the presence of 25 cancer-associated mutations between September 2013 and September 2016. They matched the women according to their ages, ethnicity and family history of cancer to assign a relative risk of developing cancer to each of the mutations.

Kurian and her colleagues found that eight of the mutations were positively associated with the development of breast cancer, and 11 were positively associated with ovarian cancer. Increased cancer risk for women carrying the mutations ranged from two to 40 times that of a woman without the mutations.

'Significant advantage'

"This large sample size provided a reliable data set on real people," said Hall. "This is a significant advantage as we work to identify the strength of association between mutation and risk."

In many cases the researchers' findings dovetailed with what had already been surmised from smaller studies. But there were some surprises. One mutation assumed to increase a woman's risk of breast cancer was shown to instead increase the likelihood of ovarian cancer. Three other mutations thought to increase the risk of breast cancer seem instead to have little effect.

"One surprising finding was the association of an increased ovarian cancer risk with mutations in a gene called ATM," said Kurian. "Although this risk was relatively small numerically, it was statistically significant, and to our knowledge it had not previously been published. Additional studies will be important to determine the robustness and clinical relevance of this finding, and to expand the evidence base that we use to counsel our patients."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Provided by Stanford University Medical Center