Risk of breast cancer mutations underestimated for Asian women, study shows

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Oncologist Allison Kurian, MD, and her colleagues at the Stanford University School of Medicine were perplexed. Computer models designed to identify women who might have dangerous genetic mutations that increase their risk of breast and ovarian cancer worked well for white women. But they seemed to be less reliable for another ethnic group.

"We've been repeatedly surprised when Asian women who the models predicted would probably not have the mutations do in fact have them," said Kurian. She recently showed that in a head-to-head comparison between whites and Asians, two of the most commonly used models failed in predicting the presence of mutations in almost half of the Asian women studied.

"Doctors and patients should have a higher level of suspicion when using these prediction models in Asian women, because they under-predicted the true number of clinically important mutations," said Kurian. "We may have to consider more subtle patterns of family cancer history when considering genetic testing in this ethnic group."

Kurian, assistant professor of oncology and of health research and policy, is the first author of the research, which was published online in the *Journal of Clinical Oncology* on Sept 8.

Mutations in two genes - BRCA1 and BRCA2 - are strongly associated with the development of breast or ovarian cancer in carriers. However, not every woman with a family history of cancer or who develops these cancers has these mutations.

To determine who should be tested for the mutations, genetic counselors frequently use computer models that assess specific variables for each woman, such as the number of relatives affected by breast and ovarian cancer, the age of each relative at onset of the condition and how closely the woman is related to her affected relatives. Those women deemed by the models to be likely carriers of these mutations are referred for testing of their BRCA1 and BRCA2 genes.

Kurian and her colleagues used two of the most widely used computer models, named BRCAPRO and Myriad II, to predict the presence of the mutations in 200 white women and 200 Asian-American women at cancer genetics clinics in four locations: Stanford, the University of California-San Francisco, Queen's Medical Center in Honolulu and the British Columbia Cancer Center in Vancouver. They sequenced the BRCA1 and BRCA2 genes of all of the study subjects and compared them to the models' predictions.

The researchers found that the models were highly accurate in predicting the presence of mutations in white women; one program identified 24 of the 25 women with BRCA1 or BRCA2 mutations and the other identified all 25. However, both programs performed much worse in predicting the 49 Asian women in the study sample with mutations. One program predicted that only 25 of the 49 women would carry mutations, while the other recommended testing of 26 women.

"It's clear that these models are far from foolproof," said Kurian, who is also a member of the Stanford Cancer Center. "These results emphasize the need for expert evaluation by a genetics professional to guide all

clinical genetic testing."

Because the Asian and white women reported similar numbers of affected relatives on average, it's possible that fewer Asians with the mutations go on to develop cancer. In that case, the family history would be a less accurate way to determine the presence of the mutations. Kurian and her colleagues are collaborating with researchers in Hong Kong to investigate these and other alternatives.

The study results point out the need for further investigation into the genetic variability of different ethnic groups. In addition to previously identified, clinically important mutations of the genes, the researchers identified more "variants of unknown significance" in the BRCA1 and BRCA2 genes of Asian women than in white women.

Many of these variants probably don't have any clinical effect," said Kurian. "We know a lot more about the normal variability of these genes in white women. Many of these variants are probably just normal for members of a particular ethnic group, but we haven't studied enough people in ethnic minority groups to know for sure, and further research needs to be done to distinguish variants of uncertain significance from truly harmful mutations."

Source: Stanford University Medical Center