Triple-negative breast cancer patients should undergo genetic screening

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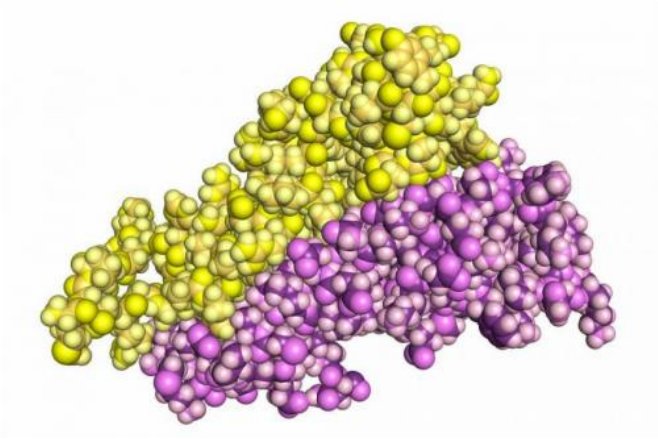

Most patients with triple-negative breast cancer should undergo genetic testing for mutations in known breast cancer predisposition genes, including BRCA1 and BRCA2, a Mayo Clinic-led study has found. The findings come from the largest analysis to date of genetic mutations in this aggressive form of breast cancer. The results of the research appear in the *Journal of Clinical Oncology*.

"Clinicians need to think hard about screening all their triple-negative patients for mutations because there is a lot of value in learning that information, both in terms of the risk of recurrence to the individual and the risk to family members. In addition, there may be very specific therapeutic benefits of knowing if you have a mutation in a particular gene," says Fergus Couch, Ph.D., professor of laboratory medicine and pathology at Mayo Clinic and lead author of the study.

The study found that almost 15 percent of triple-negative breast cancer patients had deleterious (harmful) mutations in predisposition genes. The vast majority of these mutations appeared in genes involved in the repair of DNA damage, suggesting that the origins of triple-negative breast cancer may be different from other forms of the disease. The study also provides evidence in support of the National Comprehensive Cancer Network (NCCN) guidelines for genetic testing of triple-negative breast cancer patients.

Triple-negative breast cancer is a specific subset of breast cancer that makes up about 12 to 15 percent of all cases. The disease is difficult to treat because the tumors are missing the estrogen, progesterone and HER-2 receptors that are the target of the most common and most effective forms of therapy. However, recent studies have suggested that triple-negative breast cancer patients might harbor genetic mutations that make them more likely to respond to alternative treatments like cisplatin, a chemotherapy agent, or PARP inhibitors, anti-cancer agents that inhibit the poly (ADP-ribose) polymerase (PARP) family of enzymes.

Dr. Couch and his colleagues decided to assess the frequency of mutations in predisposition genes in patients with triple-negative breast cancer to further delineate the role of genetic screening for individuals with the disease. The researchers sequenced DNA from 1,824 triple-negative breast cancer cases seen at 12 oncology clinics in the U.S. and Europe, as part of the Triple-Negative Breast Cancer Consortium.

They found deleterious mutations in almost 15 percent of triple-negative breast cancer patients. Of these, 11 percent had mutations in the BRCA1 and BRCA2 genes and the rest had mutations in 15 other predisposition genes, including the DNA repair genes PALB2, BARD1, and RAD51C. No mutations were found in predisposition genes involved in other processes like the cell cycle.

"Triple-negative breast cancers are different from all the other breast cancers," says Dr. Couch. "Other studies have suggested that this form of the

disease might be associated with some defect in DNA repair, and our study verifies that. Our findings generate a whole new set of hypotheses about how triple-negative breast cancer might be arising, which could give us better ideas for prevention or new therapies for this disease."

The study also found that individuals with mutations in predisposition genes were diagnosed at an earlier age and had higher-grade tumors than those without mutations. The researchers used their dataset to assess whether the current screening guidelines would identify all the triple-negative individuals with mutations in the two most common predisposition genes, BRCA1 and BRCA2.

They found that the NCCN guidelines, which recommend screening when there is a family history of cancer or a diagnosis under age 60, missed only 1 percent of patients carrying mutations. In contrast, the UK's National Institute for Clinical Excellence (NICE) guidelines, which use the probability of actually finding a mutation to determine who should be tested, missed 24 percent of mutation carriers.

"Our results confirm that the NCCN guidelines are good, and provide evidence to support what they have recommended," says Dr. Couch. "But we think the NICE guidelines could be expanded to include more of the triple-negative breast cancer patients with mutations."

Provided by Mayo Clinic