Mutations in susceptibility genes common in younger African American women with breast cancer

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A high percentage of African-American women with breast cancer who were evaluated at a university cancer-risk clinic were found to carry inherited genetic mutations that increase their risk for breast cancer.

The finding suggests that inherited mutations may be more common than anticipated in this understudied group and may partially explain why African-Americans more often develop early onset and "triple-negative" breast cancer, an aggressive and difficult-to-treat form of the disease.

It also demonstrates the potential benefits of increased access to genetic counseling and testing for women with breast cancer and their close relatives. Through these services, family members who are found to share the same genetic risk factor for breast cancer can be offered personalized strategies for early detection and prevention of breast cancer.

"Our study confirms the importance of screening for mutations in breast cancer susceptibility genes in all African-American breast cancer patients diagnosed by age 45, those with a family history of breast or ovarian cancer, or with triple-negative breast cancer before age 60," said study author Jane Churpek, MD, assistant professor of medicine at the University of Chicago Medicine. "This could identify at-risk family members in time for life-saving interventions and help prevent future cancers for the patients as well."

The study, to be presented June 3 at the 2013 Annual Meeting of the American Society of Clinical Oncology in Chicago, is the first comprehensive screening among African-American women of all 18 known breast cancer susceptibility genes using new methods called targeted genomic capture and next-generation sequencing.

The researchers found that 56 of the 249 women studied (22 percent) at the University of Chicago Medicine's Cancer Risk Clinic had inherited at least one damaging mutation that increased their risk of breast cancer. Twenty-six of the patients had a BRCA1 mutation. Another 20 patients had a BRCA2 mutation. Twelve women inherited mutations in other genes: CHEK2, PALB2, ATM, and PTEN. Two women inherited mutations in two different genes.

Patients most likely to carry a mutation were those diagnosed with a second primary tumor—a second cancer that developed independently from the first; 49 percent of those women carried an inherited breast cancer-associated gene mutation. Other groups highly likely to carry inherited mutations included those with a close relative who had either breast or ovarian cancer (30 percent), those with triple-negative breast cancer (30 percent), and those who were diagnosed with breast cancer by age 45 (27 percent).

Identifying these inherited mutations can have a significant impact. Whereas 12 percent of women in the general population will develop breast cancer by age 80, those carrying a harmful mutation in BRCA1 or BRCA2 have a 37 to 85 percent lifetime risk of developing breast cancer. Mutations in these genes provide the best tools for tailoring risk-reducing interventions.

The authors caution that the patients in this study are not a typical cross-section of African-American women. Two-thirds of them were referred to the cancer-risk clinic for genetic evaluation, often due to a family

history of breast cancer. Not all of them, however, had this significant risk factor. Forty percent of the 249 patients had no family history of breast or ovarian cancer, yet the researchers found damaging mutations in 12 percent of those patients.

"We expected the women in our study to have a higher risk of carrying an inherited mutation than typical breast cancer patients," Churpek said, "but some of their risk factors—diagnosis by age 45 or triple-negative breast cancer—also are more common among African-American women."

Once diagnosed with breast cancer, African-American women have lower survival rates. Regional variations in survival suggest that much of the difference may be driven by reduced access to screening and optimal care, but there is mounting evidence, including this study, that differences in tumor biology, such as a higher rate of inherited mutations in genes that increase the risk of aggressive forms of breast cancer, also play a role. In those cases, delay of diagnosis can prove deadly.

This study also demonstrates the advantages of next-generation sequencing approaches,which are faster and cost-efficient ways to use one test to look for multiple variants in many genes in many people. This approach is particularly valuable for studying patients of African heritage who tend to have greater genetic diversity. The drawback to the assay is uncertainty about how to make sense of the large numbers of sequence variations that may have no meaningful clinical significance.

"In every population, but especially among those with greater genetic diversity, we often detect changes in genes that may not yet have been studied clinically," Churpek said. "Some people question the utility of using gene panels like BROCA, as we don't always know how to counsel a patient without sufficient data on the clinical consequence of every variant found, but unless we start learning about them now we will never

know."

"What you don't know can hurt you," said study co-author Olufunmilayo Olopade, MD, the Walter L. Palmer distinguished service professor of medicine and human genetics and director of the center for clinical cancer genetics at the University of Chicago. "Women with known BRCA1, BRCA2 or other inherited mutations can lower their risk of dying from breast or ovarian cancer." Options include removing healthy ovaries by age 40 to reduce breast and ovarian cancer risk, preventive surgical removal of the breasts, or participating in a breast-surveillance protocol designed for women at increased risk.

The researchers at the University of Chicago cancer-risk clinic are testing new ways to protect women found to carry gene abnormalities that put them at risk. In a related study, also presented at ASCO, medical oncologist Rodrigo Guindalini, MD, a visiting scholar from Brazil working in the Olopade laboratory, and colleagues confirmed that a screening approach that combines MRI scans every six months with an annual mammogram can be effective. The researchers followed 222 patients for an average of 3.2 years. Half of the participants were mutation carriers and one-fifth had been treated for breast cancer.

During the study, 11 cancers were screen-detected: six by MRI, one by mammogram and four by both. All of the cancers were stage 0 or 1—the earliest, most treatable and curable stages. The average tumor size was less than 1 centimeter. None had spread to the lymph nodes.

These encouraging results may become an alternative to prophylactic mastectomy for those at the highest risk of developing breast cancer.

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