Alterations in LRIG1 gene may increase the risk for breast cancer relapse and death

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(Medical Xpress)—Women whose early-stage breast cancers had reduced numbers of copies of the LRIG1 gene were more likely to have a relapse or die of their disease, according to data published in *Cancer Research*, a journal of the American Association for Cancer Research.

"Tumors with metastatic capability have cells within them that have stem cell-like properties, which resist chemotherapy, tend to sit quietly in the tumor, and are most likely the source of metastatic spread," said Patricia A. Thompson, Ph.D., an associate professor in the Department of Cellular and Molecular Medicine and leader of the Cancer Prevention and Control Program at the University of Arizona Cancer Center in Tucson. "LRIG1 is a protein that is thought to control the growth of these cells and keep them quiet."

Human cells have two copies of most genes. An increase or decrease in copy-number of certain genes is implicated in several diseases, including cancer.

Among women who were diagnosed with stage 1 or stage 2 breast cancers, those whose tumors had loss of LRIG1 copy-numbers were almost twofold more likely to have a relapse, 2.39-fold more likely to have a relapse five years after diagnosis or later, and 1.55-fold more likely to die of their disease, compared with those whose tumors did not have loss of LRIG1 copy-numbers. Stage 1 and stage 2 breast cancers are generally considered to be at a lower risk for a relapse. These results could help clinicians identify those at increased risk and monitor them

more carefully.

"First, we found that the loss of LRIG1 gene copy-numbers in tumors of early-stage patients was associated with a higher risk of disease relapse, metastasis, and death," said Thompson. "Second, we observed that the patients whose tumors had an increase in the copy-numbers of LRIG1 had much better clinical and pathology characteristics, generally. This suggested that the gain of LRIG1 copy-numbers may contribute to the lower risk observed in these patients."

Thompson and colleagues used breast cancer tissue samples from 971 women who were treated at MD Anderson Cancer Center for stage 1 or stage 2 breast cancers between 1985 and 2000. This analysis was a joint collaboration between investigators at MD Anderson Cancer Center and the Baylor College of Medicine in Houston, and the University of Umeå in Sweden.

They used a high-resolution molecular inversion probe array with 300,000 probes, 12 of which detected alterations in LRIG1. This technology is best suited for samples that have been stored for long periods of time and was vital for this project, said Thompson.

Of the 971 samples, 3.7 percent had gain, and 8.9 percent had losses in LRIG1 copy-numbers. The researchers also found that LRIG1 copy-number loss was more common in triple-negative (13.8 percent) and HER2-positive (12.3 percent) breast cancers, which have worse prognosis, compared with luminal A and luminal B subtypes (less than 10 percent).

LRIG1 copy-number loss was also more prevalent in samples from black and Hispanic women (12.8 and 12.2 percent, respectively), who often have worse breast cancer outcomes, compared with samples from non-Hispanic white women (7.7 percent).

The researchers found that LRIG1 copy-number loss was significantly associated with disease relapse, distant metastasis, and death.

The researchers next used data from pooled, publicly available data sets yielding 1,576 samples to analyze alterations in LRIG1 and found that low expression of this gene was associated with increased distant metastasis and death, compared with medium or high expression. "Given that these results are such a strong replication of our findings from really old samples, we were very excited," said Thompson.

Outcomes from these two analyses did not change even after adjusting for known factors that influence relapse and metastasis, leading the researchers to conclude that alteration in LRIG1 copy-numbers is an independent risk factor for breast cancer metastasis and death in otherwise low-risk patients.

"Measurement of the expression levels of LRIG1 as RNA or protein would be more clinically relevant and we would like to see the development of such an assay," said Thompson. "Efforts in developing LRIG1 as a tumor marker would help in developing new agents to kill or silence these cells as a means to prevent breast cancer relapse and metastasis.

"Our ability to identify patients as being at high risk for relapse versus at those at very low risk is dramatically improving," Thompson added.

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