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# Researchers link gene expression patterns of normal tissue to breast cancer prognosis

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Breast tissue surrounding tumors could be used to gauge future survival outcomes for women with estrogen receptor-positive breast cancer, a study led by University of North Carolina Lineberger Comprehensive Cancer Center researchers has found.

In the journal *NPJ Breast Cancer*, researchers reported they identified a particular gene expression pattern in normal-appearing breast tissue around tumors that was linked to lower 10-year survival rates for women with estrogen receptor-positive breast cancer.

Based on the finding, the researchers believe they could use gene expression patterns – identified using genomic sequencing—in normal, adjacent tissue to predict survival for patients with that type of breast cancer. This is significant because, according to the National Cancer Institute, approximately 70 percent of breast cancers are estrogen receptor-positive.

"Most of the studies to-date that have tried to develop predictive biomarkers for cancer progression have focused on tumor cells themselves," said the study's first author Melissa Troester, PhD, a UNC Lineberger member and an associate professor in the UNC Gillings School of Global Public Health Department of Epidemiology. "This suggests that other factors in the microenvironment of the tumor may be important in predicting prognosis."

The findings were drawn from what researchers say is the most

comprehensive genetic and molecular analysis to-date of normal-appearing tissue surrounding breast cancer tumors. Advances in large-scale, faster sequencing of DNA and RNA made the study possible, they said.

For the study, researchers analyzed multiple genomic characteristics of normal-appearing tissue, including DNA mutations, repeat copies of genes, DNA methylation and miRNA and gene expression patterns. The samples were drawn from The Cancer Genome Atlas, a multi-institution, collaborative effort backed by federal research dollars to map genomic and epigenomic alterations driving cancer.

"Normal tissues do not get the same attention as tumor samples," said co-author Katherine Hoadley, PhD, a UNC Lineberger member and research assistant professor in the UNC School of Medicine Department of Genetics. "This analysis allowed us to look more closely at whether these normal-looking tissues were actually molecularly normal. What we found was in many samples, there was evidence of tumor or changes in the tissue. It is interesting that no single genomic analysis consistently identified defects in the adjacent breast tissue, highlighting the difficulty in finding these alterations."

Of the samples examined by multiple genomic methods, about 40 percent had some type of DNA or RNA defect in the normal tissue outside the tumor margin. Researchers believe that using genomic methods, they identified cancer cells or defective normal cells that were undetected using the microscope. However, the presence of cells with defects was not linked to better or worse survival for patients.

"Breast cancer researchers have recognized that likely, breast-conserving therapy is leaving behind tissue or cells that are either partially or fully transformed," Troester said. "But these cells are targeted by therapy after surgery, keeping recurrence rates low for breast-conserving therapy."

Troester said that this finding highlights the benefit of radiation therapy, which has been shown to lower recurrence rates for women who chose breast-conserving surgery. It also reaffirms studies that found no benefit to wider surgical margins during surgery—since they found cells with genetic defects as far away as 4 centimeters from the tumor.

"This says it's not sufficient to just excise the tumor with the wider margin – those mutations are still present at even farther distances from the tumor," Troester said. "This tells us that radiotherapy and adjuvant chemotherapy are pretty effective in eliminating cells with those DNA defects."

They also analyzed the gene expression patterns of the normal tissue outside tumor margins. Based on an analysis of mRNA and microRNA expression patterns, they found two different subtypes of tissue near the tumor. In women with estrogen receptor-positive cancer, one of the subtypes was linked to significantly lower 10-year survival rates.

"Gene expression subtypes of the surrounding tissue may reflect the composition and biological activity of the breast tissue in those patients," Troester said. People with the subtype linked to the worse overall survival may have more fat in their tissue, or have higher cancer-driving signaling.

"This suggests that it may be possible to add information from the tumor microenvironment to standard clinical information to predict prognosis for patients," Troester said.

**More information:** Hui Li et al. Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA data set, *npj Breast Cancer* (2016). DOI: 10.1038/npjbcancer.2016.12