

Tumor-free breast tissue can have precancerous changes

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A new study using mastectomy tissue shows that precancerous changes can occur in normal-appearing areas of the breast as distant as two inches from a tumor's edge.

The findings, while preliminary, might have important implications for identifying breast-cancer patients at high risk of a second tumor in the same breast.

Researchers looked for – and found – a chemical change called DNA methylation in healthy tissue adjacent to breast tumors.

They measured this chemical change in a gene that often becomes highly methylated in breast cancer. The gene, called RASSF1A, is a tumor-suppressor gene. Tumor-suppressor genes normally protect cells from becoming cancerous, but the gradual silencing of these genes by abnormal methylation is thought to be an early change in cancer development.

In addition, the study identified three other genes that were abnormally methylated in both tumor and normal tissues.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute and at H. Lee Moffitt Cancer Center and Research Institute, is published in a recent issue of the journal *Clinical Cancer Research*.

"This is evidence that DNA methylation is a very early event in tumor development, and that genes that are methylated might serve as useful markers for early cancer detection and diagnosis," says principal investigator Tim H-M. Huang, professor of molecular virology, immunology and medical genetics with Ohio State's Comprehensive Cancer Center.

"Our study might also help explain why, in the absence of radiation therapy, breast cancer often recurs near the site of the original tumor following a lumpectomy," says first author Pearly S. Yan, research assistant professor of molecular virology, immunology and medical genetics and a researcher and a researcher in Huang's laboratory. Lumpectomy is a surgical procedure in which only the tumor tissue is removed.

If the findings are verified in more patients, they might lead to a prognostic test that could help doctors estimate a woman's risk of cancer recurring near the surgical site.

Evidence began emerging 10 years ago that the healthy tissue adjacent to breast tumors may show precancerous changes, but the means to study the question comprehensively were not available until recently.

During this study, the researchers measured the degrees of methylation in tissue removed from 47 patients who had undergone mastectomies for a form of breast cancer called invasive ductal carcinoma. This tissue was compared with 69 samples of normal tissue taken up to four centimeters (almost two inches) from the tumor's visible edge and with control tissues removed during breast-reduction surgery.

The study also included two double-mastectomy cases in which both breasts had been removed to prevent cancer recurrence. For these, the researchers also tested tissue from four locations on the breast that had

no visible tumor.

The researchers used microdissection techniques to isolate tiny milk ducts in each sample. They then measured methylation levels in the RASSF1A gene in epithelial cells that lined the ducts. These cells were the sources of the initial tumor.

As expected, tumor cells showed the highest methylation levels. But the researchers found significant methylation levels in normal tissue adjacent to the tumors in 29 patients. The degree of methylation was lower than in the tumor cells, but it was 1.75 times higher than in control cells.

"In both double-mastectomy cases, we were surprised to find high methylation levels in the tumor-free breast," says Yan.

In addition, the researchers identified three other genes (called CYP26A1, KCNAB1 and SNCA) that were highly methylated in about one-third to nearly one-half of the breast tumors.

"Again to our surprise, we found that in 70 percent of cases, when these genes were highly methylated in tumor cells, they were also highly methylated in the adjacent normal tissue," says Yan.

"This suggests that the presence of DNA methylation in normal tissue adjacent to tumors is more prevalent than previously thought."

Next, the researchers will study whether the abnormal chemical change in normal tissues adjacent to tumors is associated with local recurrence.

Source: Ohio State University

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