Molecular 'clock' could predict risk for developing breast cancer

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Dr. David Euhus has helped determine that methylation acts as a type of biological clock, indicating how many times a cell has divided. The chemical reaction in genes could one day help researchers more accurately determine a woman's risk for developing breast cancer and provide a new approach for treatment. Credit: UT Southwestern Medical Center

A chemical reaction in genes that control breast cancer provides a molecular clock that could one day help researchers more accurately determine a woman's risk for developing breast cancer and provide a new approach for treatment, UT Southwestern Medical Center

researchers have found.

In a study published in today's issue of *Cancer Epidemiology Biomarkers & Prevention*, scientists from UT Southwestern show that the chemical process, called methylation, is strongly correlated with breast-cancer risk and with precancerous changes in the breast cells.

The researchers determined that methylation acts as a type of biological clock, indicating how many times a cell has divided. This information could aid researchers in determining an individual's cancer risk.

"The more a cell has divided, the greater the risk for cancer," said Dr. David Euhus, professor of surgical oncology. "Monitoring methylation levels could give researchers a way of seeing how often cells have divided and where a woman stands on that clock. Once the clock reaches a certain hour, breast cancer is more likely to ensue."

During methylation, small molecules called methyl groups attach themselves to a gene and turn off, or "silence," the gene.

Previous studies by Dr. Euhus have shown that apparently normal breast cells from women with breast cancer had increased methylation of a tumor-suppressor gene called RASSF1A.

In the current study, Dr. Euhus wanted to see if methylation of RASSF1A and other genes increased over time during the years when the ovaries are actively secreting estrogen and progesterone each month.

Dr. Euhus and his team sampled cells from 164 women – women with breast cancer, women at high risk of developing breast cancer, and women with a low risk for the disease. The researchers examined methylation levels of five tumor-suppressor genes whose job is to stop tumors from developing in the breast.

A computer program developed by Dr. Euhus was used to determine the breast-cancer risk for patients in the study. Dr. Euhus has written several interactive software tools for risk measurement, which are used by major cancer centers worldwide.

His findings indicate that methylation of RASSF1A and other genes increases steadily during the years of ovarian cycling – up to about age 55 – suggesting that methylation is, indeed, a molecular clock recording the history of cell divisions.

“Interestingly, having children, which is known to reduce breast-cancer risk if it occurs early in life, was associated with a reduction in methylation for some genes,” Dr. Euhus said.

Dr. Euhus says the clock is not always marching forward, and there are ways to turn it back.

“Methylation can be stopped or slowed down,” said Dr. Euhus, who also directs the Mary L. Brown Breast Cancer Genetics and Risk Assessment Program at the Harold C. Simmons Comprehensive Cancer Center. “We found that having a baby set the clock backward and so did getting close to menopause. Things that are known to reduce breast-cancer risk may also turn the clock backward.”

A test for methylation of tumor-suppressor genes is not commercially available and Dr. Euhus says additional research is necessary to fully understand the mechanism. For example, it is not clear whether tumor-suppressor gene methylation is simply a marker of prior cell divisions, or whether it can cause increased cell division, hastening the development of breast cancer.

Dr. Euhus said medications that interfere with methylation might provide a new approach for reducing breast-cancer risk.

“Even if there’s a lot of methylation, I can’t tell for sure if a woman is going to develop breast cancer,” Dr. Euhus said. “However, if I took two women from our study and one had more methylation than the other, the one with more methylation was more likely to have already had breast biopsies for benign disease, or had already been diagnosed with breast cancer.”

Measuring tumor-suppressor gene methylation might not work well to predict breast-cancer risk in all women. For women with a strong family history of breast cancer, the concept won’t work because those breast cancers are associated with DNA repair issues and not methylation, Dr. Euhus said.

Source: UT Southwestern Medical Center