MedicalXpress

Breast cancer risks acquired in pregnancy may pass to next three generations

September 11 2012

Chemicals or foods that raise estrogen levels during pregnancy may increase cancer risk in daughters, granddaughters, and even great-granddaughters, according to scientists from Virginia Tech and Georgetown University.

Pregnant rats on a diet supplemented with synthetic estrogen or with fat, which increases estrogen levels, produce ensuing generations of daughters that appear to be healthy, but harbor a greater than normal risk for mammary cancer, the researchers report in today's *Nature Communications*.

Although the findings have not yet been validated in humans, the study shows that environmental damage may be passed from one generation to the next not through genetic mutations, but through "epigenetic" alterations that influence how genomic information is decoded.

The research also raises hope that people who may be especially sensitive to carcinogens can be identified and novel prevention strategies can be employed before cancer strikes.

"We have shown for the first time that altered DNA methylations modulated by specific diet in normal development are heritable and transgenerational," said Yue "Joseph" Wang, the Grant A. Dove Professor of Electrical and Computer Engineering at Virginia Tech Research Center – Arlington. "We also identified key methylation alteration sites that may be involved or responsible for increased breast

cancer risk, which may serve as novel biomarkers for scientists to develop novel and targeted prevention strategies."

The National Cancer Institute estimates that more than 226,000 women and more than 2,000 men will develop breast cancer in 2012, and nearly 40,000 people will die of the disease.

Two thirds of breast cancers that occur in families have no known genetic cause, according to Leena Hilakivi-Clarke, a professor of oncology at Georgetown Lombardi Comprehensive Cancer Center. The study shows what may be underlying the cancer are not genetic mutations, but inherited effects of maternal intake of high-fat diets and exposure to excess estrogen during pregnancy.

"It is becoming clear that the process of epigenetic signaling—which genes are expressed and which genes are silenced—is being affected by a mother's hormonal environment during pregnancy," said Hilakivi-Clarke, who has studied the effects of maternal diet on offspring in animals and humans for more than 20 years. "The early studies indicate in a normal pregnancy a woman may have more than 20 different estrogen levels, and the highest and the lowest all result in a healthy baby. The challenge has been to understand how something in fetal development can affect breast cancer risk more than 50 years later."

The study was led by Sonia de Assis, a postdoctoral researcher in Hilakivi-Clarke's laboratory at the Georgetown Lombardi Comprehensive Cancer Center at Georgetown University Medical Center.

Virginia Tech researchers developed mathematical models and machine-learning techniques to analyze the changes in DNA methylation status in the descending daughters to understand how increased cancer risk is transmitted without genetic mutation.

DNA methylation is a key process in normal development, allowing cells with the same genome to perform different functions by adding chemical groups to DNA to turn some genes on and some genes off.

Wang's group found that the descendants with increased risk had several hundred common DNA regions that were methylated differently than in a control group, providing statistically convincing evidence that breast cancer risk can be transmitted via epigenetic means.

"Ultimately, it may be possible to undo or prevent this harmful methylation and decrease the risk of breast cancer." Wang said. "A next step will be to study the timing of the intervention and the impacts of the methylation as it occurs in the early, middle or end of the pregnancy. The promising news is pharmacologic or other interventions may be able to reverse the harmful exposure."

Provided by Virginia Tech