Molecular changes with age in normal breast tissue are linked to cancer-related changes

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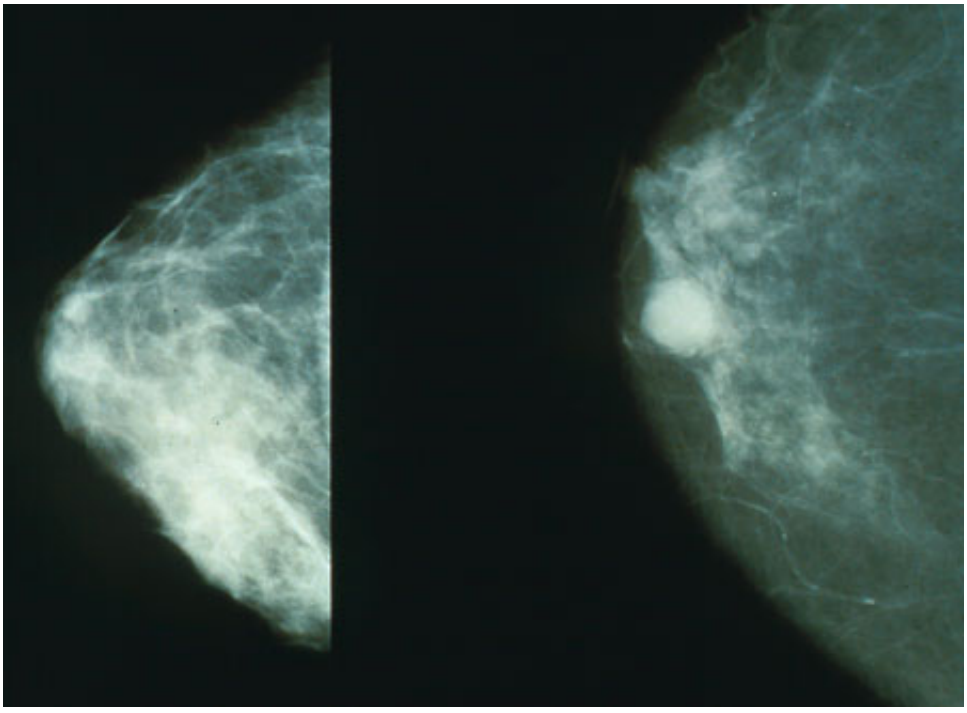

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Several known factors are associated with a higher risk of breast cancer including increasing age, being overweight after menopause, alcohol intake, and family history. However, the underlying biologic mechanisms through which many of these recognized breast cancer risk factors contribute to onset of disease remains unclear. A new study led by Brock Christensen, PhD, with first author Kevin Johnson, PhD, at

Dartmouth's Norris Cotton Cancer Center provides insight into how changes that occur with age may predispose breast tissue cells to becoming cancerous. Specifically, the Dartmouth study demonstrates that age is the breast cancer risk factor most strongly associated with normal breast DNA methylation differences, and regions in the genome where DNA methylation changes occur with age are particularly sensitive to disruption in cancer. Taken together, this new data provides insight into how epigenetic dysregulation with age in normal breast tissue itself may contribute to breast cancer risk.

"Our group and others have previously shown that epigenetic modifications such as DNA methylation are early events in breast carcinogenesis," said Christensen. "In this work, we measured DNA methylation in normal breast tissue samples from disease-free women to investigate whether changes in DNA methylation underlie the biologic effects of known breast cancer risk factors." Their study, "Normal breast tissue DNA methylation differences at regulatory elements are associated with the cancer risk factor age" was recently published in *Breast Cancer Research*.

What makes this research innovative is that it seeks to characterize those molecular differences in healthy normal tissues that are associated with cancer risk factors. "Previous studies have examined DNA methylation patterns in populations with invasive breast cancer, and we have examined epigenetic profiles of pre-invasive (early stage) breast cancers," explained Christensen. "However, this work focused on normal breast tissue donated by disease-free subjects who provided robust risk factor data, allowing us to investigate genome-scale DNA methylation in healthy tissue from subjects across a wide range of ages."

This research was not without challenges, both with technology and resources. Access to normal breast tissues from disease-free women requires an invasive biopsy procedure and such specimens are not

typically available, particularly in conjunction with risk factor data. The team acquired these precious samples by submitting a proposal to the Susan G. Komen Foundation Tissue Bank to access their biospecimen resources. Once they received approval for the project, they sought to resolve some technical challenges. Breast tissues include a mixture of cell types, each with their own cell-type DNA methylation pattern, so the researchers applied leading-edge computational methods to account for potential differences in cellular proportions across samples using the resources available through Discovery: the Dartmouth high-performance computing cluster.

Looking ahead, the team hopes that this work provides a foundation that will better position future studies to evaluate how modifiable risk factors or disease prevention interventions may reduce age-related risk. Future studies aimed at better understanding the mechanisms of these newly identified epigenetic changes are also needed. Next steps for the Dartmouth-led team include diving further into studying the impact of modifiable influences on the early stages of breast cancer. "Ideally, a larger prospective study of normal breast tissue would increase our ability to identify those women at the greatest risk of breast cancer," said Christensen. "Given the challenges of procuring breast tissue and risk factor data, we're pursuing studies of DNA from cells in breast milk as it's a tissue-specific specimen, can be obtained without invasive procedures, and is available during a critical window that shapes both short- and long-term risk of breast cancer."

More information: Kevin C. Johnson et al, Normal breast tissue DNA methylation differences at regulatory elements are associated with the cancer risk factor age, *Breast Cancer Research* (2017). DOI: 10.1186/s13058-017-0873-y

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