Changes in breast tissue increase cancer risk for older women

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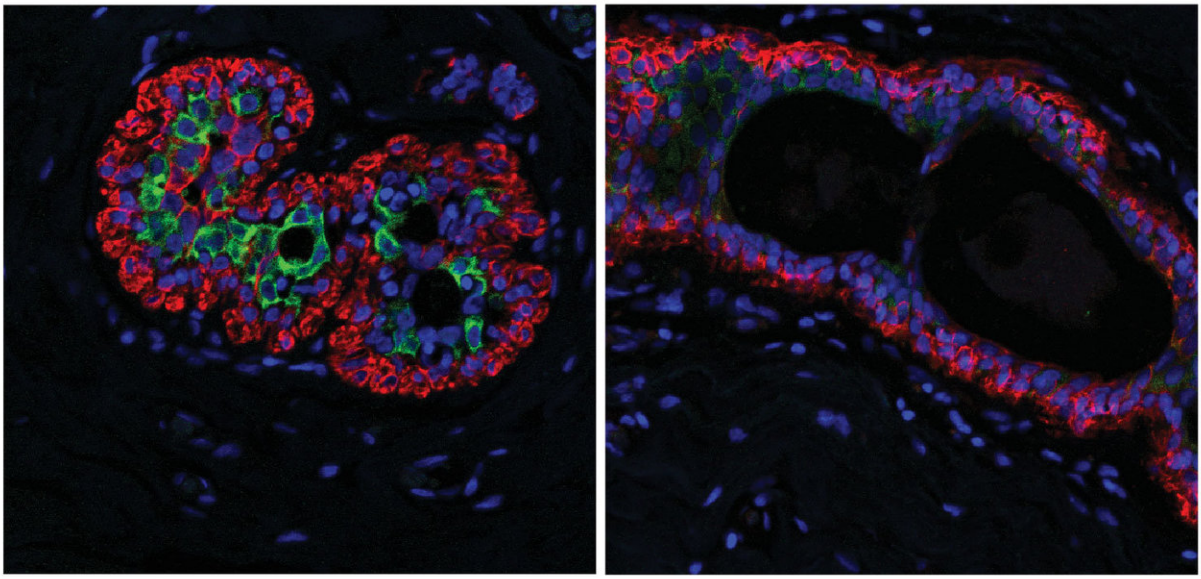

Breast sections of a 17 (left) and a 58 year old woman (right) stained for a luminal marker (green) and a myoepithelial/basal marker (red). The luminal cells lose fidelity with age which causes them to appear less luminal and more basal. High-dimensional analysis pinpointed this key age-related change in the luminal population, which may be associated with higher breast cancer risk. Credit: Jonathan K Lee in the lab of Dr. Mark LaBarge

Researchers in Norway, Switzerland, and the United States have identified age-related differences in breast tissue that contribute to older women's increased risk of developing breast cancer. The findings,

published April 24 in the journal *Cell Reports*, may help scientists better understand how breast cells change during the aging process, enabling doctors to catch the signs of cancer earlier.

Previous studies have shown that, as women age, the composition of their breast tissue changes. Multipotent progenitors—cells with the ability to develop into more than one type of cell—build up in the body. These findings strengthen suspicions that the influx of progenitor cells can lead to cancer.

"We hypothesized that accumulation of those progenitors is one of the mechanisms that underlies increased susceptibility to breast cancer with age," says Mark LaBarge, a professor of population sciences at City of Hope. "We saw a glimpse of this in past data, but this is the first study to identify these age-related differences at such high resolution."

The international team led by James Lorens, a professor of biomedicine at University of Bergen, looked at cells from 56 women and found that, as the age of the subject increases and multipotent progenitor cells accumulate in the epithelial layer of breast tissue, they develop into defective luminal (inner epithelial) cells. These defective luminal cells look more like the myoepithelial (outer) cells, giving the entire luminal layer a less consistent appearance. Meanwhile, the proportion of myoepithelial cells—which suppress tumors—diminishes.

"We were able to show that the age-related luminal cells were derived from defective luminal progenitors that also accumulate with age," Lorens says. "This study gave us a much deeper picture of the changes that happen with age and displayed the impressive heterogeneity that comprises the mammary epithelium." The team was also able to identify a protein signature that emerges in aging breast cells—a finding that they believe may be directly related to older women's increased susceptibility to breast cancer.

Changes in the appearance of aging cells—and the health threats those changes can pose—are not unique to breast tissue. Researchers have found similar age-related differences with cells in the bone marrow and brain. "Accumulation of stem/progenitor cells with skewed differentiation and function may be a hallmark of aging in a number of tissues," says first author Fanny Pelissier Vatter.

The researchers analyzed data from the cell samples by using algorithms to create a virtual map of epithelial cell phenotypes, with more similar-looking cells grouped more closely together. These visual groupings allowed the team to identify minute changes in breast tissues of different ages and suggested how cells that look different might be related. They were also able to assign women to their correct age group using algorithms based on the types of epithelial cells present in their tissue—a demonstration of just how strongly these cellular differences correlate with age. The exception was a small cell sample from a group of young women carrying the BRCA1 gene, which puts them at an unusually high risk of developing breast cancer. Their cells more closely resembled those of the older women.

The researchers believe they can help doctors prevent cancer by providing them with a better understanding of how breast tissue and its surrounding microenvironment are altered as women grow older. "Mapping the changing cellular phenotypes during aging, and connecting these to early cancer phenotypes, could identify potential points of intervention," says Lorens.

More information: *Cell Reports*, Pelissier Vatter et al. "High-Dimensional Phenotyping Identifies Age-Emergent Cells in Human Mammary Epithelia." DOI: 10.1016/j.celrep.2018.03.114