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Breast specific ELF5 clock for the risk assessment to Breast Cancer

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Breast Cancer (BC) is the most common cancer among women in the U.S. A robust BC prevention strategy requires risk assessment biomarkers for early detection. More than 75% of BC diagnoses occur in women over 50 years of age, suggesting that aging is the greatest risk factor for BC. However, biomarkers that are currently used are unable to precisely measure an older individual's physiological or functional age. Thus, we are motivated to identify a biomarker to predict the risk of BC and simultaneously develop a prevention tool. During aging in the human mammary gland, luminal epithelial cells lose lineage fidelity as evidenced by decreased expression of luminal lineage-specific genes and increased expression of markers unique to myoepithelial cells. One prominent feature of the loss of luminal lineage fidelity with age is the downregulation of luminal-specific ELF5 gene expression with increased DNA methylation on its promoter. ELF5 is central to the maintenance of healthy luminal epithelial cells and shows age-dependent changes that parallel changes seen in age-related BC. We have reported that both ELF5 expression and methylation can be used to build biological clocks to estimate the chronological ages of mammary epithelia. ELF5-clock-based estimates of biological age in luminal epithelia from average-risk women were within three years of chronological age. Using the same clock, the biological ages of breast epithelia from BRCA1 or BRCA2 mutation carriers, who have a high risk of developing BC, are accelerated by two decades relative to chronological age. Our finding indicates that the changes in ELF5 expression or ELF5-proximal DNA methylation in luminal epithelia are emergent properties of at-risk breast tissue and constitute a breast-specific biological clock.

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