

NIH study finds epigenetic ‘clocks’ can aid prediction of breast cancer risk

By Stacy Lawrence, Staff Writer

Genetics can only tell us so much when it comes to understanding cancer. It turns out that interrogating the myriad processes involved in the translation of DNA into actual bodily processes, as well as alterations over time, are crucial. To that end, researchers at the NIH are pursuing a more refined understanding of epigenetics, which is defined by how biochemical processes work to modify gene expression.

Researchers from the National Institute of Environmental Health Sciences (NIEHS), part of NIH, used a trio of different measures of DNA methylation known as epigenetic clocks. Each clock measures methylation found at differing, specific locations in the genome. DNA methylation modifies the functions of genes and affects gene expression, without altering DNA itself, and it is associated with aging as well as external environmental stressors and factors.

Against the clock

The clocks offer an assessment of ‘biologic age’ that takes those environmental issues into account vs. simple chronological age. The latest study found that for every five years of acceleration in biologic age as compared to chronological age, that is associated with a 15 percent increase in breast cancer risk. The results were published online on Feb. 22, 2019, in the *Journal of the National Cancer Institute*.

“We went in with some skepticism that the epigenetics clocks would differ between women who developed breast cancer and in women who didn’t develop breast cancer. So, the fact that all three of them show a difference – and that the women who developed breast cancer have an increased biologic age on the clocks, compared to women who didn’t develop breast cancer – was surprising to us, as was the degree of effect,” said the study’s corresponding author Jack Taylor, head of the NIEHS Molecular and Genetic Epidemiology Group. “A five-year acceleration would result in a 15 percent increase in breast cancer; a 10-year acceleration would result in a 30 percent increase.”

The study of DNA methylation was based on blood tests in 2,764 women, a subset of the more than 50,000-subject Sister Study that monitors sisters of women who have already been diagnosed with cancer but do not have cancer themselves. Of those, 1,566 women developed incident breast cancer with pathology reports obtained for those women.

Each epigenetic clock is designed to measure DNA methylation

at distinct points in the genome. Two of the clocks, known as Hannum and Horvath, were designed specifically around age-related DNA methylation while Levine was oriented toward changes associated with age-related diseases. That last one demonstrated the strongest association in the study.

“There’s the degree of consistency between the clocks, even though the clocks have very little overlap in terms of which sites on the DNA that they are looking at. So the clocks are largely independent of one another in terms of specific sites across the genome that they are looking at,” explained Taylor. “We know that this methylation change across the genome happens with age and that it is widespread. These clocks are each using a different subset of sites.

“Two of the clocks were developed specifically just to try to correlate with age, and the third clock, the one that showed the strongest association in our study, the Levine clock, was developed not just to predict age, but rather to predict this other measure called pheno-age,” he continued. Pheno-age was a metric that was developed by the first author of that paper, Levine, who took a number of different blood parameters that are associated with age-associated disease and put them together into a combined score that they tried to use to predict age-related mortality.

In the study, the researchers controlled for factors that were expected to bias results such as alcohol intake and body mass index (BMI), both of which are known to accelerate epigenetic age and breast cancer risk. They also adjusted for blood cell composition in the samples.

Screening risk

That research could lead to a better means of identifying at-risk disease populations, as well as who could use increased screening or preventive intervention. The expectation is that those epigenetic clocks could actually be tailored to specific chronic diseases.

Aging is related to disease onset in various chronic conditions, but those epigenetic clocks help to identify people who are in fact more or less at risk for disease because of accelerated or deferred aging. The idea is to get more information on the factors that contribute to faster biological aging, as well as to understand what characteristics and environment are associated with a biological age that lags behind an individual’s chronological age.

Next, researchers hope to continue to try to answer a series of questions around what factors cause a biologically advanced clock – and whether altering those exposures can work to advance or retard that biological clock. In addition, some people have an advanced biologic age, but that doesn't necessarily then translate into disease. Taylor said he is curious about why and if there are protective factors in that population. "We're getting a reasonable handle on the genetic determinants of the changes in the DNA sequence, in terms of the inherited version that we get the single nucleotide polymorphous (SNPs) – the different things that we sequence, differences that we inherit. We're just now starting to get

a handle on some of these epigenetic changes – these modifications of DNA that are not encoded in the sequence but control gene expression," said Taylor.

"DNA methylation is one of those and there are other epigenetic changes in terms of how the DNA is organized. Again, not the sequence but that control of how genes are expressed," he concluded. "We believe that environmental factors, exposures and lifestyle factors may have important consequences on those at the genome level – that may differ from tissue, so may be different in your liver than they are in your blood than they are in your heart. And those differences may be important in terms of understanding disease risk." ♦