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## Genetic clues to predicting life span

Inside chromosomes are telomeres that age as we age, and may serve as indicators of how long we'll live

By Cathryn Delude

Wrinkles may betray our age externally, but our cells divulge their age -- and chronicle life's toll -- at the tips of our chromosomes. These tips, called telomeres, may also foretell our risk of early death.

Telomeres are the protective caps made of repetitive chunks of DNA that keep the rest of the gene-laden chromosome from disastrously unraveling. But they lose bits of themselves with each cell division, so over a lifetime, like a counter, telomeres shorten. Eventually, shortened telomeres send cells into senescence, a retirement-like state in which they no longer divide or remain active but do not die.

Senescent cells in our skin make us look withered; in our immune system, they make us susceptible to the diseases of aging such as heart disease, heart failure, diabetes and what's called a "failure to thrive."

Ultimately, if we could better understand the connections between telomeres and longer, healthier lives, we might know how to protect or enhance those chromosome tips. That might not require new drugs, but simply following what we already know about a healthy lifestyle.

### Disease fighters

Most human studies on telomeres focus on white blood cells in the immune system, one of the few cell types in adults that produce an enzyme called telomerase. Telomerase maintains telomeres by adding back the DNA lost during cell division. Immune cells need telomerase so they can frequently divide and replenish themselves without losing their telomeres, said Dr. Elizabeth Blackburn, a biologist at UC San Francisco and a co-discoverer of telomeres and telomerase. But with age, telomerase diminishes, so immune cell telomeres eventually shorten.

One recent study published in the July 2008 *Journal of Arteriosclerosis, Thrombosis and Vascular Biology*, an American Heart Assn. journal, found that, among 780 patients with stable heart disease, people with the shortest telomeres in their immune cells had twice the risk of death and heart failure after 4.4 years as patients with the longest telomeres. Those in the highest-risk group had telomeres half the length of those in the lowest-risk group.

"Since we adjusted for age, we know that the telomere length is telling us something more than chronological age," said Dr. Ramin Farzaneh-Far, a cardiologist at UC San Francisco who analyzed

the data. "Hopefully it is measuring biological age."

In other words, the same factors that predispose us to chronic diseases and make us look old before our time may also make telomeres age -- shorten -- beyond their years. High levels of stress hormones, inflammation, insulin and blood sugar, as well as habits such as smoking, fatty diets, obesity and sedentary living are all linked to shorter telomeres and lower telomerase levels.

"It makes sense," said Dr. Judith Campisi, an expert on telomeres at the Buck Institute for Age Research in Novato, Calif., who was not involved in the study. "If you smoke, you're introducing oxidation into the bloodstream, and telomeres are more sensitive to oxidative stress than the rest of the genome, so they will shorten substantially. When you're stressed, your adrenal glands release stress hormones called glucocorticoids that tend to kill T-cells in the immune system. So more cells divide to replace them, and the more you drive cell proliferation, the more you wear down telomeres."

A new study appearing in the inaugural issue of *Aging* adds a new twist to the connection between lifestyle and telomere length. It went back to blood samples stored from 236 healthy 70- to 79-year-olds for the National Institutes of Health-funded MacArthur Study of Successful Aging, led by UCLA researchers. The researchers measured the telomere length from patients' 1988 samples and from the same patients' 1991 samples and then tracked how many had died of cardiovascular disease. Men with the greatest rate of telomere shortening had three times the mortality rate. For women, change mattered less than baseline: There were 2.3 times more deaths among those starting out with the shortest telomeres.

"This study suggests that before people had the disease they had short telomeres," said Dr. Elissa Epel, an assistant professor of psychiatry at UC San Francisco who was involved in this and several other telomere studies. The telomere connection suggests that in some way, short telomeres may predispose people to heart disease.

"What's the link between blood cell telomeres and heart disease?" asked Blackburn, who collaborated on this study. "We think it's based on something that's been seen before. When the immune system gets older, it gets more inflammatory, and inflammatory responses have been clearly tied to cardiovascular disease. So the fact that we see an immune system that seems to be acting more aged, judging by its shorter telomere length, is a strong smoking gun. That might be what's underlying this cardiovascular disease risk."

### What they show

Based on studies like these, some researchers think that telomere length could predict life span better than traditional measures.

"Cholesterol tests just tell you about your lipid profile, glucose tests just tell you about blood sugar, and C-reactive protein just tells you about inflammation," Epel said. "Telomere length is a more summative measure for multiple biochemical imbalances, a global marker of health status."

Dr. Robert Sapolsky, a neurology professor at the Stanford School of Medicine who was not involved in these studies, agrees. "Telomere measures are a good time-integrated marker of bad news, as opposed to those other factors being somewhat more acute." They indicate "systemic wear and tear."

But how broadly useful such a marker, which is still just a research tool, would be is unclear -- because no one knows whether telomere length in immune cells reflects those in other tissues. So while blood cells can provide relevant information about cardiovascular disease and diabetes risks, they may not indicate much about the aging brain or Alzheimer's disease.

There is good news and perhaps a lesson amid the findings about telomere length. Some people in the study actually had their telomeres lengthen instead of shorten. This study did not measure telomerase levels, but a small pilot study by Blackburn, Epel and others of 30 men published last November in the *Lancet* suggests it is possible to elevate telomerase levels naturally and reverse the ill effects of unhealthy living on telomeres. Comprehensive lifestyle improvements -- including a low-fat diet, regular exercise and stress reduction through meditation and yoga -- increased telomerase activity levels by 30% after three months.

"Unhealthy living could increase factors that damage the telomeres' DNA," said Dr. Emanuel Skordalakes, assistant professor at the Wistar Institute, an independent biomedical research institute in Philadelphia. "By living healthier they were able to increase levels of telomerase activity, which can take care of that damage and which in turn should increase the length of telomeres."

Three months was too short a time to expect to see such increases, but whether that could be a longer-term outcome that could reduce the risk of dying from a chronic disease is one of the questions that researchers are trying to answer.

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