Long telomere length associated with increased lung cancer risk

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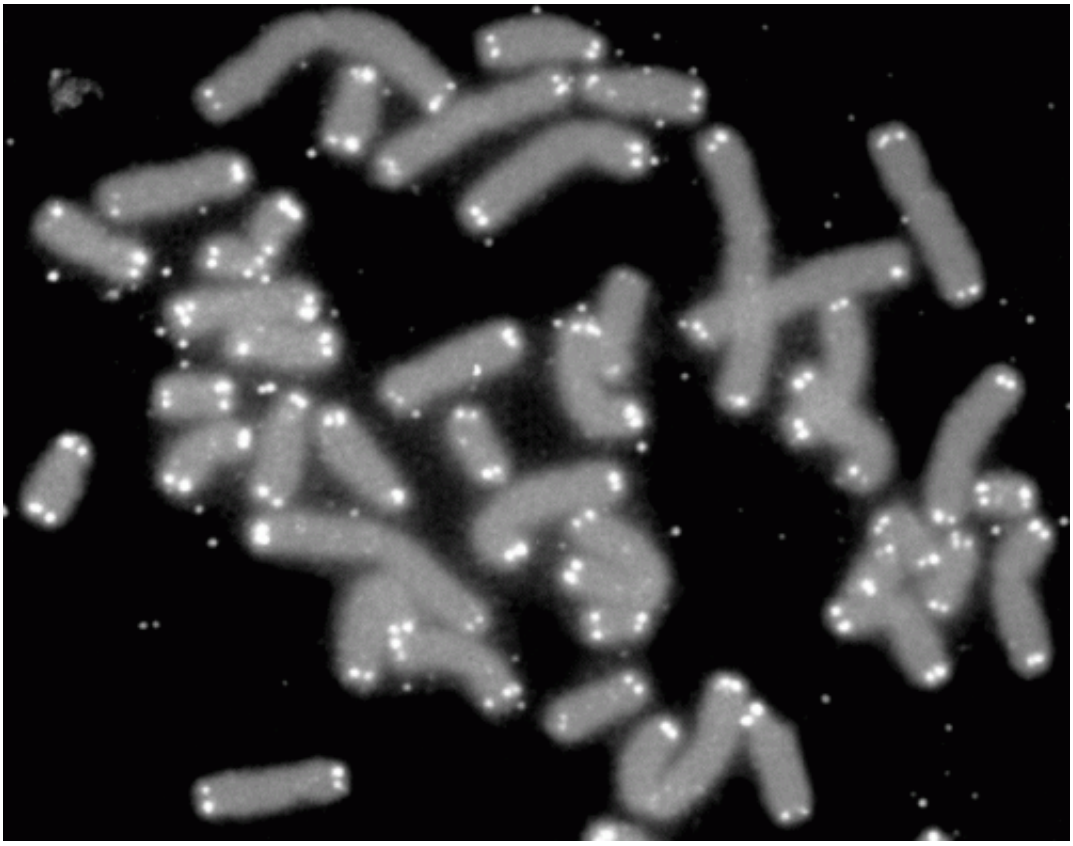

Human chromosomes (grey) capped by telomeres (white). Credit: PD-NASA; PD-USGOV-NASA

A large-scale genetic study of the links between telomere length and risk for five common cancers finds that long telomeres are associated with an increased risk of lung adenocarcinoma. No significant associations

between telomere length and other cancer types or subtypes were observed. The study, led by scientists from the University of Chicago, uses a novel method to measure genetic predisposition for telomere length, rather than physiological measures which are confounded by factors such as age and lifestyle. The findings are published in *Human Molecular Genetics* on July 29, 2015.

"Our work provides compelling evidence of a relationship between long telomeres and increased risk for lung adenocarcinoma," said study leader Brandon Pierce, PhD, assistant professor of public health sciences at the University of Chicago. "The prevailing hypothesis has been that short telomeres are bad for health, but it appears that this does not necessarily translate to some types of cancer."

Telomeres are protective caps of DNA that prevent damage to the ends of chromosomes. A portion of the telomere DNA is lost during cell division. This leads to telomere shortening over time, which has been thought of as a time-delay "fuse" that can trigger cell death or genomic instability. Shortened telomeres have been implicated in aging and cardiovascular diseases, but their relationship with cancer risk is thus far unclear. Because telomeres can vary greatly due to factors such as age, lifestyle and cancer progression, efforts to study the direct associations between cancer risk and telomere length have been difficult.

To address this issue, Pierce and his colleagues used Mendelian randomization, a method which calculates telomere length based on genetic factors. They created a score based on a combination of genetic variants identified by prior genome-wide association studies as being associated with telomere length. Since genetics remain unchanged even as telomeres physically shorten, this measurement allowed for unbiased comparisons to cancer risk.

Using genome data from more than 50,000 cancer cases and 60,000

controls through the GAME-ON (Genetic Associations and Mechanisms in Oncology) network, the team compared telomere lengths with the risk of developing breast, lung, colorectal, ovarian and prostate cancers, including subtypes.

They found that longer telomeres were significantly associated with increased risk for lung cancer - specifically lung adenocarcinoma, which more than doubled in risk for every 1000 base pair increase in telomere length. Surprisingly, the researchers found no associations between shortened telomeres and cancer risk. Aside from lung cancer, only prostate cancer risk showed a modest positive association with long telomeres.

"Mendelian randomization is an important tool that allows us to examine telomere length without the problematic biases that come with physically measuring it," said study author Chenan Zhang, graduate student in public health sciences at the University of Chicago. "The positive association between telomere length and lung adenocarcinoma should be further investigated with the long term goal of improving prediction and prevention of this common cancer subtype."

The team suggests a potential explanation for this observation is that long telomeres enable more rounds of cell division than short telomeres, which could allow cells to live longer and have more opportunities to accumulate carcinogenic mutations.

While their results shed light on the unclear role of telomeres in cancer biology, Pierce and his colleagues warn that Mendelian randomization produces estimates of causal relationships, but the estimates could be biased if the genetic variants measured in the study affect cancer risk and telomere length independently.

However, the method holds significant advantages and has successfully

been used to investigate associations such as those between heart disease and cholesterol types. The team is now examining telomere length in additional populations to evaluate whether some groups based on age, gender, smoking history and other factors may be at additional increased risk.

"The complex relationship between telomeres and cancer risk is one that we need to further understand," Pierce said. "This study gives us an estimate of a causal relationship that could serve as a guidepost for the development of interventions in the future."

More information: "Genetic determinants of telomere length and risk of common cancers: a Mendelian randomization study," *Human Molecular Genetics*, 2015.

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