Accelerated biological aging may cause bowel cancer

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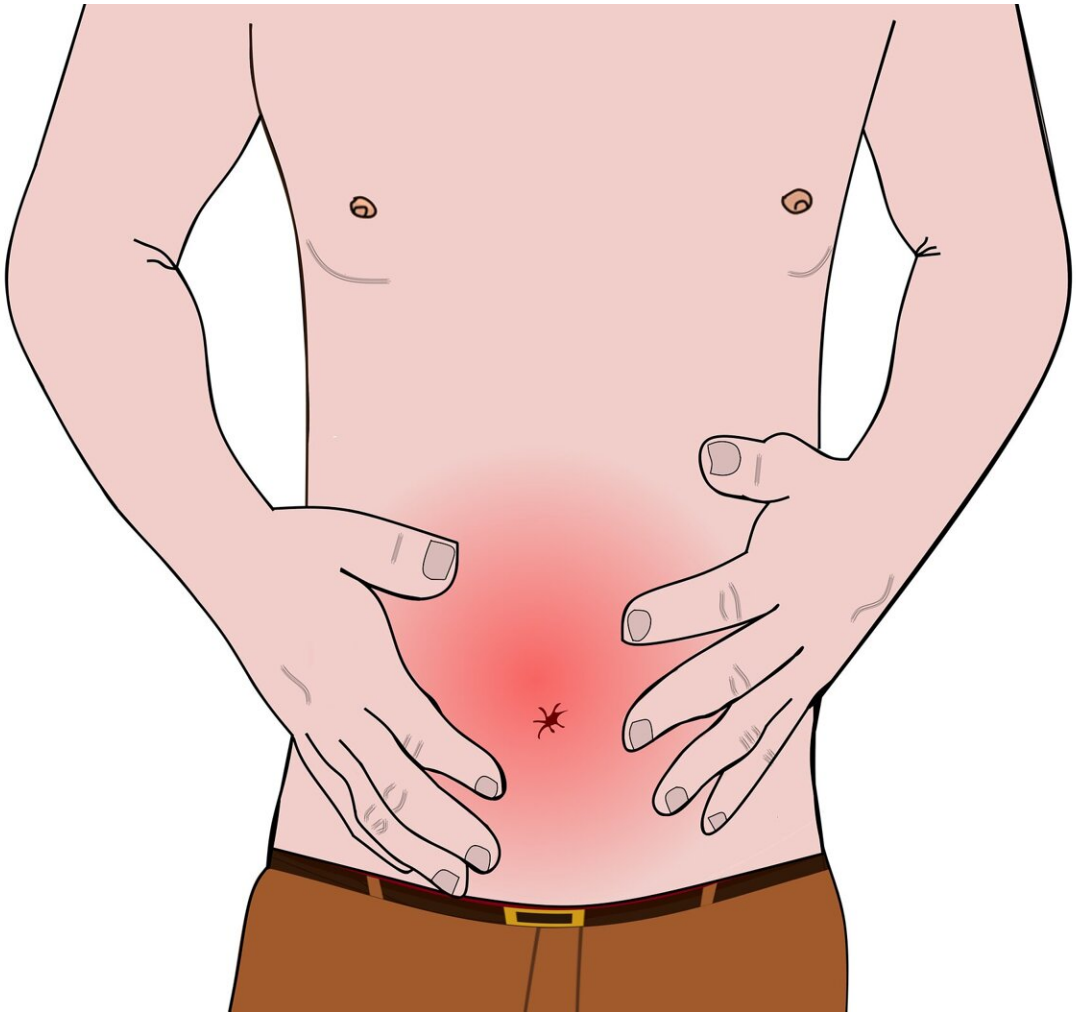

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Scientists have shown how accelerated biological aging measured by an epigenetic clock may increase the risk of bowel cancer, according to a report published today in *eLife*.

The study provides evidence that biological age might play a causal role in the increased risk of certain diseases, and paves the way for interventions that could slow down this process.

Epigenetic markers are changes to DNA which may alter the way in which our genes work and are known to vary as we age. A type of epigenetic marker called DNA methylation is often used to measure age. DNA methylation patterns on the genome have been shown to relate closely with age and they can provide insights into "biological aging"—that is, how old our cells look compared to how old they are in years.

"When an individual's biological age is older than their chronological age, they are said to be experiencing epigenetic age acceleration," explains first author Fernanda Morales-Berstein, a Wellcome Trust Ph.D. Student in Molecular, Genetic and Lifecourse Epidemiology at the MRC Integrative Epidemiology Unit, University of Bristol. "Epigenetic age acceleration, as measured by DNA methylation-based predictors of age called epigenetic clocks have been associated with several adverse health outcomes including cancer. But although epigenetics can be used to predict cancer risk or detect the disease early, it is still unclear whether accelerated epigenetic aging is a cause of cancer."

Making a causal link between biological clocks and disease is challenging because it is hard to know whether biological aging increases the risk of disease, or whether other independent factors raise the risk of a disease and biological aging at the same time. To address this, the team used a method called Mendelian randomization to mimic a randomized trial evaluating the effectiveness of changes in epigenetic aging as a

cancer prevention strategy. They used information on known genetic variants associated with levels of epigenetic age acceleration to investigate this.

The team compared four established epigenetic clocks used to measure biological aging and their genetically predicted associations with a range of cancer types. Two were first-generation clocks which use patterns of DNA methylation strongly linked to chronological age. The others were second-generation clocks which use markers associated with increased risk of age-related diseases or death.

They found limited evidence that accelerated epigenetic age is causally linked to breast, lung, ovarian or prostate cancer.

The most striking result was seen for bowel cancer, where the results measured by one of the second-generation clocks, called GrimAge, suggested a 12% increased risk of bowel cancer with every additional year of biological age (over chronological age). These results were further corroborated by an association between biological age acceleration and parental history of bowel cancer. Further analysis suggested that evidence for the risk was stronger for colon cancer compared with rectal cancer.

Previous studies have suggested that epigenetic age acceleration is influenced by several cancer risk factors, such as obesity and smoking. The additional evidence from the current study suggests that targeting this pathway, for example through lifestyle changes or epigenetic-targeted therapies, could help reduce this risk.

"Our work provides potentially relevant findings for public health," says senior author Dr. Rebecca Richmond, Vice-Chancellor's Research Fellow in Molecular Epidemiology at Bristol's MRC Integrative Epidemiology Unit.

"If epigenetic age acceleration is a causal mediator between risk factors and bowel cancer, the clock may be a treatable intermediary for when targeting the underlying risk factors is not feasible or too difficult to accomplish, particularly in populations at high risk. More research is needed to support our findings and evaluate whether epigenetic age acceleration can be modified by lifestyle or clinical interventions."

More information: Fernanda Morales Berstein et al, Assessing the causal role of epigenetic clocks in the development of multiple cancers: a Mendelian randomization study, *eLife* (2022). DOI: 10.7554/eLife.75374

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