

# Tissue samples show the deep genetic and cellular impacts of smoking

March 14 2024

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It's no secret that smoking is extremely detrimental to health. Tobacco smoke contains thousands of chemicals, including carcinogens, increasing the risk of cancer, cardiovascular and respiratory diseases.

A new study from the University of Chicago analyzed data from more than 900 samples of nine different human tissue types to understand just how deep the cellular and genetic damage from smoking goes. The research team generated epigenetic data to assess the effects of smoking on DNA methylation, or genetic locations where a handful of atoms can attach to DNA and turn off [gene expression](#).

They found several new regions associated with smoking, including some that are shared across tissue types, suggesting that DNA methylation is part of the body's attempts to defend itself from the damaging effects of [tobacco smoke](#).

The paper, "The association of cigarette smoking with DNA methylation and gene expression in human tissue samples," was [published](#) March 14, 2024, in the *American Journal of Human Genetics*.

## **Exposures affect more than the blood**

Epidemiological studies on the effects of exposure to chemicals and other environmental contaminants like smoke often use only [blood samples](#), mostly because they are easy to collect. For this new study, senior author Brandon Pierce, Ph.D., Professor of Public Health Sciences and Human Genetics at UChicago, and his team worked with samples from the GTEx Project, a biobank housing human tissue samples from more than 950 postmortem tissue donors. The team used DNA methylation data from nine tissue types, including lung, colon, ovary, prostate, whole blood, breast, testis, kidney, and muscle.

"If we want to understand the effects of environmental exposures like smoking, it's important to study a variety of tissue types, in addition to blood, because disease occurs in many different organs in the body," Pierce said. "The epigenome varies dramatically across [cell types](#) and tissue types, as could the epigenetic effects of exposures."

The [tissue samples](#) also came with data about whether the donor ever smoked in their lifetime (i.e. "ever smokers"), if they never smoked (never smokers), or they were currently smoking at the time of death (current smokers).

The team analyzed data on DNA methylation at cytosine-guanine (CpG) dinucleotides, or regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in the sequence of bases. They found 6,350 smoking associated CpGs in [lung tissues](#), and 2,753 in colon tissues, meaning that these genetic regions showed differences in DNA methylation among the ever or current smokers, compared to never smokers.

Doing this same kind of analysis in blood samples only reflects the effects of smoking on [immune cells](#), whereas analyses in non-blood tissues gives researchers a new window into its health impacts.

"When we do our multi-tissue study, it gives a way more comprehensive understanding of how smoking affects the human body," said James Li, the study's co-first author and an MD/Ph.D. student in the Department of Public Health Sciences. "I think our work is super exciting because we had the power to directly examine the effects of smoking in tissues such as lung and colon, which are highly relevant in the pathophysiology of smoking."

## **Understanding defense mechanisms to smoke**

Many of the CpGs identified in the tissues matched up with ones identified in previous studies using blood samples, including genes involved in detoxification or transformation of foreign chemicals so they can be removed from the body. There were big differences among [tissue types](#) too, however.

The lungs have nearly three times as many smoking-associated CpGs identified as the colon, for example, which makes sense because the lungs are directly exposed to [cigarette smoke](#).

"Each tissue is exposed to smoking in a different way. The lung is much more direct through inhalation, whereas the colon comes later. So, that's a different nature of exposure, and we can capture the effects of that difference," said Niyati Jain, co-first author and a Ph.D. student in the Committee on Genetics, Genomics, and Systems Biology.

While we certainly don't need more evidence that smoking is bad for health, this [tissue](#)-specific understanding of its effects does help understand what's happening at a cellular level, and how the body responds to exposure.

"The epigenetic responses to smoking may reflect mechanisms that defend us against or mediate the adverse effects of smoking. Characterizing them can give us a better understanding of disease relevance and risk," Jain said.

In addition to smoking, Pierce said he can envision using the same technique to understand other, less obvious, environmental exposures. "We can identify epigenetic signatures that can serve as biomarkers of exposure effects. For example, based on a person's epigenome, we can potentially tell if they've been exposed to a particular type of contaminant," he said. "The more we can increase the diversity of tissues and number of samples from more people, the more we can learn."

**More information:** The association of cigarette smoking with DNA methylation and gene expression in human tissue samples, *The American Journal of Human Genetics* (2024). [DOI: 10.1016/j.ajhg.2024.02.012](https://doi.org/10.1016/j.ajhg.2024.02.012).

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Provided by University of Chicago

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