Medical Xpress

Large-scale study explores genetic link between colorectal cancer and meat intake

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Credit: AI-generated image

In one of the largest ever gene-environment interaction studies of red meat and colorectal cancer, which explored the impact of red meat consumption on a person's cancer risk based on their genotype, researchers have identified two genetic markers that may help explain the association between the two and explain why some people face a

higher cancer risk.

Past studies show that frequently consuming red and processed meat increases the risk of developing colorectal cancer, but the predominant biological mechanism is not yet established. Understanding the disease process and what genes underlie it can help scientists develop better prevention strategies.

A new study supported by the National Institutes of Health and led by the USC Norris Comprehensive Cancer Center, part of the Keck School of Medicine of USC, analyzed data on red and processed meat intake from 29,842 people with colorectal cancer and 39,635 people without cancer. It found that those who consumed more red or processed meat faced, respectively, a 30 or 40% increased risk for colorectal cancer.

Using genome-wide data, the researchers also identified two genes, HAS2 and SMAD7, that altered cancer risk levels based on red or processed meat consumption levels. The results were published in Cancer Epidemiology, Biomarkers & Prevention.

"These findings suggest that there's a subset of the population that faces an even higher risk of colorectal cancer if they eat red or processed meat," said lead author Mariana C. Stern, Ph.D., a professor of population and public health sciences and urology, the Ira Goodman Chair in Cancer Research and the associate director for population science at the USC Norris Comprehensive Cancer Center.

"It also allows us to get a peek at the potential mechanism behind that risk, which we can then follow up with experimental studies."

The researchers used a combination of standard methods to pinpoint gene-environment interactions, as well as a new statistical approach developed in the Keck School of Medicine's division of biostatistics by

co-authors William James Gauderman, Ph.D., a professor of population and public health sciences, Juan Pablo Lewinger, Ph.D. and Eric Kawaguchi, Ph.D., both assistant professors of population and public health sciences and their colleagues.

"These state-of-the-art statistical methods and software allowed us to maximize efficiency as we tested for gene-meat interactions across seven million genetic variants," Gauderman said.

The risk of red and processed meat

The analysis included data from 27 studies of colorectal cancer risk in people of European origin. Gauderman and Ulrike Peters, Ph.D., MPH, a professor and the associate director of the public health sciences division at the Fred Hutchinson Cancer Center in Seattle, compiled data from the Genetics and Epidemiology of Colorectal Cancer Consortium, the Colorectal Cancer Transdisciplinary Study and the Colon Cancer Family Registry.

First, the research team harmonized data from various studies to create standard measures for the consumption of red meat (beef, pork, and lamb) and processed meat (bacon, sausages, luncheon/deli meats, and hot dogs). For each category, they calculated servings per day, adjusted for body mass index, and divided participants into four groups based on levels of red or processed meat intake.

People with the highest level of red meat intake had a 30% increased risk for colorectal cancer; those with the highest level of processed meat intake had a 40% increased risk. These findings do not account for genetic variability that may put some people in the population at higher risk than others.

Genetic markers of cancer risk

Next, based on DNA samples, the researchers compiled data for over seven million gene variants spanning the genome for each study participant. They then conducted a genome-wide gene-environment interaction analysis of the link between red meat intake and cancer risk. Looking at each position in the genome—known as a single nucleotide polymorphism (SNP)—they asked whether having a certain gene variant altered the risk of getting colorectal cancer for people who ate more red meat.

At almost every SNP on the genome, the answer was no. Regardless of what gene variant a person had, their cancer risk based on red meat consumption stayed the same. However, at two specific SNPs, the association changed.

Using a standard statistical analysis approach, the researchers flagged rs4871179 SNP in chromosome 8 near the HAS2 gene. The gene, which is part of a pathway that codes for protein modification inside cells, has been linked to colorectal cancer in some previous studies but never to red meat consumption.

The analysis showed that people with a common variant of the HAS2 gene found in 66% of the population faced a 38% higher risk of colorectal cancer if they consumed the highest level of meat. In contrast, people with another, rarer variant of the same gene had no increased risk of cancer when they ate more red meat.

"We then used our novel, two-step machine learning approach first to identify patterns among SNPs, red meat consumption, and cancer, then focus on the most promising combinations in our gene-environment interaction tests," Gauderman said.

This method flagged rs35352860 SNP in chromosome 18, part of the SMAD7 gene. SMAD7 regulates hepcidin, a protein linked to iron metabolism. Because red and processed meats contain high levels of heme iron, the researchers hypothesize that different variants of SMAD7 may increase cancer risk by changing the way the body processes iron.

"When hepcidin is dysregulated, that can lead to increased iron absorption and even iron overload inside cells," Stern said.

People with two copies of the most common variant of the SMAD7 gene present in about 74% of the population faced an 18% greater risk of colorectal cancer if they ate high levels of red meat. Individuals with only one copy of the most common variant or two copies of a less common variant had substantially higher cancer risk—35% and 46%, respectively.

"These findings suggest that different genetic variants may confer a differing risk of colorectal cancer in individuals who consume red meat and highlight possible explanations for how the disease develops," said Joel Sanchez Mendez, a doctoral student in the Keck School of Medicine's department of population and public health sciences and a co-author of the study.

More evidence needed

The findings reveal promising new details about the link between meat consumption and colorectal cancer, but Stern stresses that they do not yet prove a causal link for these genetic variants.

"This gives us some important food for thought," she said. "We do these gene-environment interaction studies when we know there's a clear association between an environmental exposure and a disease, but what happens in between is still a black box."

Next, she and her colleagues hope to follow up with experimental studies that could provide stronger evidence for the role of dysregulated iron metabolism in the development of colorectal cancer.

More information: Mariana C. Stern et al, Genome-Wide Gene–Environment Interaction Analyses to Understand the Relationship between Red Meat and Processed Meat Intake and Colorectal Cancer Risk, *Cancer Epidemiology, Biomarkers & Prevention* (2023). DOI: 10.1158/1055-9965.EPI-23-0717

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