Large-scale study finds new genetic risk factors for colorectal cancer, paving the way for better screening, prevention

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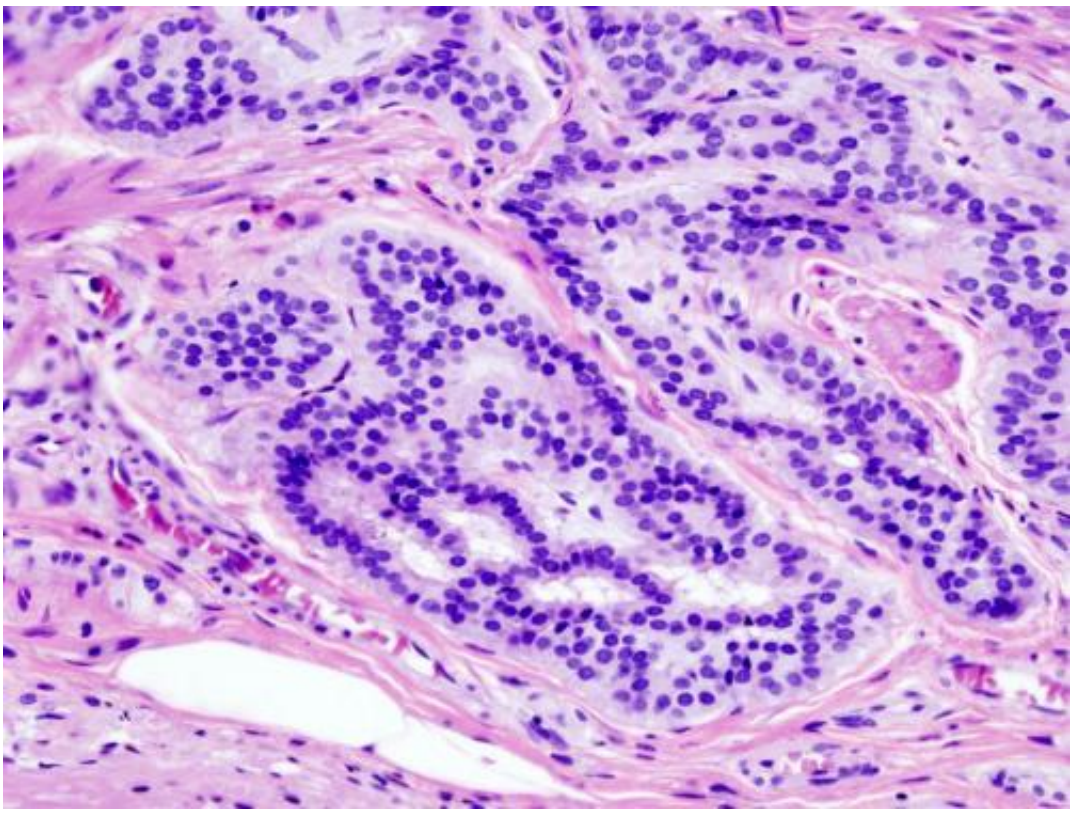

Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

A comprehensive analysis of more than 100,000 colorectal cancer (CRC) cases, led by researchers at the Fred Hutchinson Cancer Center in

Seattle and 200 scientific collaborators worldwide, has identified more than 100 new genetic risk factors strongly linked with the disease.

These findings, published Dec. 20 in the journal *Nature Genetics*, could help clinicians better determine who's at highest risk for colorectal cancer so they can receive early screening. It may also help to identify potential candidates for preventive chemotherapy or other proactive treatments.

According to study authors, these findings demonstrate the power of big data—combining such a large-scale study with complex, detailed analysis using multi-omics, to gain additional insights into the underlying biology of colorectal cancer. Multi-omics is a biological analysis approach that combines multiple large-scale biological data sets "omes," such as the genome, proteome and transcriptome, etc.

"This is the largest, most comprehensive study to date of common genetic risk factors for colorectal cancer," said Dr. Ulrike "Riki" Peters, molecular and genetic epidemiologist with Fred Hutch and a corresponding lead author of the study. "We're excited about our study's discoveries, including the addition of 100-plus genetic risk variants for this severe disease."

Our previous research had identified about 140 genetic markers for colorectal cancer, added Peters, whose research focuses on the genetic and environmental risk factors for colorectal cancer, as well as on the impact of race and ethnicity on underlying genetic risk factors for common, complex diseases.

For this study, the researchers conducted a meta-analysis of more than 100,000 colorectal cancer cases compared with a control group of more than 150,000 people without the disease. Both groups were of European or Asian ancestry.

Their initial findings identified 205 independent risk associations for colorectal cancer, of which 50 had not been previously reported. Further multi-omics analysis revealed an additional 53 gene variants linked to the disease.

"Our findings provide new insights into colorectal cancer and substantially expand our knowledge of the role gene variation plays in inherited colorectal cancer," said Dr. Li Hsu, a biostatistician with Fred Hutch and shared fist author on the study.

Germline genetic risks or gene mutations—those you inherit from your biological parents—play a vital role in cancer risk and susceptibility.

"Knowing these hereditary factors and which groups are at greatest risk from them can guide clinicians in recommending preventive measures and more frequent screenings which can lead to earlier diagnosis and treatment and better survival outcomes for patients." as pointed out by Dr. Minta Thomas one of the first shared authors on the paper and staff scientist at the Fred Hutch working with Drs. Hsu and Peters.

Colorectal cancer affects approximately 1.9 million people worldwide annually and is a leading cause of death around the globe. In the U.S., colorectal cancer is the third most diagnosed cancer, excluding skin cancers, according to the American Cancer Society. Overall, the lifetime risk of developing CRC is about 1 in 23 or 4.3% for men and 1 in 25 or 4% for women.

"Colorectal cancer is a serious disease, but it is preventable and can be successfully treated if detected early," said Dr. William Grady, director of the GI Cancer Prevention Program Clinic and a professor at Fred Hutch. "This study has the potential to pave the way for better screening and prevention, allowing us to improve our current ways of determining who is at higher risk."

This study findings also validated more commonly known risk factors for CRC, including insulin resistance, smoking and obesity, that have been observed and reported in previous epidemiological studies.

Fred Hutch and its research collaborators plan to use the study's findings to develop tests based on germline DNA that can categorize who's at high genetic risk for colorectal cancer—and who may have only minimal likelihood for developing the disease.

A longer-term goal is to combine genetic risk data with other risk factors—environmental, dietary and behavioral (such as smoking)—to create multifaceted risk scores, known as polygenic risk scores, that more precisely pinpoint a person's colorectal cancer risk.

"Overall, our findings demonstrate the power of multi-omic analysis to provide new insights into the biological basis of colorectal cancer, including the identification of specific gene mutations and support for previously unsuspected functional mechanisms," said Peters. "Several of the genes and pathways we identified are potential targets for preventive therapy."

More information: Deciphering colorectal cancer genetics through multi-omic analysis of 100,204 cases and 154,587 controls of European and East Asian ancestries, *Nature Genetics* (2022).

Provided by Fred Hutchinson Cancer Center