TuSalud

Using Genetic Data to Overcome Disparities in Colon Cancer Rates

The new collaboration will dig into tumor genome, microbiome to address colon cancer inequities among people of color.

October 7, 2020 By Diane Mapes

When actor Chadwick Boseman died of metastatic colorectal cancer at the tender age of 43, the country was shocked. Public health scientists at Fred Hutchinson Cancer Research were less surprised.

For years, epidemiologists and other researchers have known certain racial and ethnic groups are far more likely to be diagnosed with, and die of, colorectal cancer than others, particularly African Americans and Alaska Natives. The latter group has the highest rates of this cancer in the world, an alarming disparity that's remained unchanged for 30 years.

Now, with the help of a three-year, $3.6 million grant from the National Cancer Institute, a team of Hutch public health researchers will lead a collaboration to try to close this gap, which they're calling the Translational Research Program in Colorectal Cancer Disparities.

It will mark the first deep genetic dive into the tumor DNA and RNA, along with the tumor microbial content of three understudied populations: African Americans, Hispanics and Alaska Natives.

Currently, 40 out of every 100,000 white people are diagnosed with colorectal cancer and 16 of those people die. In African Americans, the incidence rate is 49 out of 100,000 and 21 of those people die. In Alaska Natives, the incidence rate is 91 per 100,000 (more than double the cancer incidence of whites) and 38 of those patients end up dying (again, more than twice that of whites). While Hispanics have a lower rate overall, they're often diagnosed at a younger age, as are many Black and Indigenous people.

"The differences are staggering," said Tabitha Harrison, a Hutch genetic epidemiologist and the new collaboration's administrator.

The team hopes to pinpoint exactly what's driving these poor colorectal cancer outcomes in people of color. Part of it is due to structural racism and lack of access — to preventive screenings, to insurance, to a trusted health care provider. (Read more about Fred Hutch health disparities research.)

But molecular and genetic epidemiologist Dr. Riki Peters, one of three principal investigators on the grant, believes there's more to it.

"An increasing number of epidemiological and biologic studies show that it is not only structural racism," she said. "It's complex. I'm expecting there are multiple factors contributing to these high mortality rates. Even the microbiome could have an effect on the gene expression profile," [i.e., how genes are turned on and off]. "We have to look at all of it."

Building trust, gathering data

Colorectal cancers are influenced by many things: diet, lifestyle factors, medical history and genetics. While the microbiome may also be a factor in colorectal development, research on that is limited.

Also limited, or just plain lacking: research on people of color. The scientists want to remedy that with a comprehensive genetic analysis of tumor tissue samples from these understudied populations. They hope their work will not only lead to new molecular targets and drugs that can attack them, but a better system of preventive care for at-risk groups.

The ambitious collaboration is the result of years of preparation and collaboration between Peters, Harrison, fellow principal investigator Dr. Christopher Li, Fred Hutch researchers Drs. Susan Bullman, Amanda Phipps and Bill Grady, and others within and without the Hutch.

"This has been building over many years," said Peters, whose Genetic and Epidemiology of Colorectal Cancer Consortium, or GECCO, has already pinpointed a number of genetic risk factors and variants associated with colorectal cancer that have helped to identify those most at risk. "We've done a lot of pilot studies to even get to this stage. There is a lot of trust building with a project like this. You have to prove yourself first. You have to build the research framework."

The Hutch will partner with the Alaska Native Tribal Health Consortium (ANTHC research director Dr. Timothy Thomas is the new project's third principal investigator); Cedars-Sinai, a nonprofit hospital in Los Angeles; and the Ochsner Health System, a nonprofit health care provider based in southeast Louisiana.

All of the research will be informed by an external advisory board, an internal advisory board and a community advisory board made up of colorectal patients of color, representatives from community-based organizations and other stakeholders.

"It's important to have voices of the diverse community," said Peters. "We definitely want the community advisory board to be reflective of the patient population we're looking at."

Drilling down into the genetic data

Each of the four partner institution will provide around 200 tumor tissue biospecimens from a group of patients, all of whom were diagnosed, treated and either survived or succumbed to colorectal cancer. Tumor tissue and healthy tissue samples from Alaska Natives will come from the

ANTHC, Hispanic patients' samples from Cedars-Sinai and African Americans' from Ochsner. As a comparison group, the researchers will include the same number of samples from non-Hispanic white cancer patients recruited to the study by Dr. Polly Newcomb of Fred Hutch.

"This will be the first study to molecularly characterize colorectal cancer tumors from Alaska Native people," said Harrison. "We're happy to be able to collaborate and partner with the ANTHC to do this work. It's very exciting."

The tissue samples will go through DNA and RNA sequencing to better understand the genetic data. (RNA, like DNA, is a type of genetic material, and sequencing RNA in addition to DNA provides important information about how genes are turned on in the body.) Such genetic characterization finds all the variations and variants in DNA sequences or specific genes in a person's body that can lead to disease.

Identifying these variants and the cellular pathways — or instructions — they activate can also pave the way for prevention and treatment.

"It's hard to attribute why we're seeing differences," said Harrison. "And it's a mistake to attribute it to lifestyle reasons or biological reasons when you haven't characterized it."

Springboard for more disparities research

The biological data will be used for two new research projects and any others that might arise from this NCI grant, known as a "mini-SPORE," or Specialized Program of Research Excellence. The grant was awarded to the Hutch in preparation for a larger, more comprehensive SPORE focusing on cancer disparities.

SPOREs are large study grants on steroids — hefty projects that pull in multiple institutions and investigators and allow for more innovation and a faster translation of interventions into clinical use.

"SPOREs allow us to bring in a broader research community to tackle questions more holistically," said Peters, who holds the Fred Hutch 40th Anniversary Endowed Chair. "That's the major advantage. You can have a diversity of expertise and backgrounds to really drill down into the problem. There's a lot of synergy. You can start thinking much more outside the box."

The new "mini-SPORE" grant covers the creation of an administration core, a biospecimen and pathology core, and a developmental research program to identify research questions to be proposed as full projects in their future SPORE application.

"By collecting this material and creating a biospecimen bank, we're creating an opportunity for others to do research on racially and ethnically diverse populations," said Harrison. "The sequenced tumor tissue microarrays will be made available for others to use."

Multiple populations, multiple perspectives

Li, an epidemiologist who also serves as faculty director of the Hutch Office of Diversity, Equity & Inclusion, said the new grant will provide a slew of opportunities.

“This grant will enable us to study these populations in an unprecedented way,” he said. “We’ve also been trying to increase our capacity to do research into health disparities and this grant is an ideal mechanism to do that.”

Li said institutional and structural racism is an “important piece” of the disparities puzzle but agreed the high rate of early onset disease and/or high incidence and mortality in these groups suggests further multidisciplinary research is needed.

“This unique collaboration will bring together lab scientists, public health scientists and clinicians,” he said. “We will do work that spans the entire continuum. We’ll assess social determinants of health, molecular characteristics of tumors and the microbiome, so we can understand the disparities that are present from multiple perspectives.”

Toward that end, the grant also provides for not just a diverse mix of patients, but a diverse mix of investigators.

“A key component of the grant is to help promote the careers of early investigators, particularly underrepresented minority scientists,” he said.

A pair of studies will kick off the new grant.

The first will look for novel tumor-tissue based predictors of colorectal cancer progression and death in African Americans, Alaska Natives, Hispanics and non-Hispanic whites and assess these predictors’ potential for clinical utility, that is, to guide new strategies or therapies.

Led by Li and geneticist and physician Grady, the study will also evaluate the immune response to colorectal cancers in the different groups, comparing tumor tissue and outcomes data from Black, Hispanic/Latino and Alaska Native patients with that of non-Hispanic whites.

“We know that a strong immune response in a tumor can be very beneficial for improved survival,” said Peters. “But we really don’t know right now if our immune response differs between different ethnic groups.”

Bacteria-driven cancer?

The second study will plumb the tumor microbiome to identify its role in cancer development with an eye toward finding new treatments to target specific bacteria that might be driving colorectal cancers in people of color.

Led by Phipps, Peters and Bullman, the team will investigate the role various bacteria play in colorectal cancer, particularly that of Fusobacterium nucleatum, which previous studies show can drive precancerous lesions and result in cancers with a poorer prognosis.

Since the different groups may have substantially different dietary patterns and environmental exposures, the researchers want to see whether bacteria in the gut differ across populations and if those differences might be contributing to a higher burden of colorectal cancers.

“We’re definitely expecting differences in the gut microbiome between the four different racial/ethnic groups,” Peters said. “Dietary habits differ from group to group.”

While existing biospecimen data will be used for the first two studies, the researchers hope to also recruit participants for future research projects. Results from these initial studies will most likely be available in three years, Harrison said.

The larger goal of eliminating bias — in genetics, in research, in the clinic and in society — will take longer. But it’s crucial for the health of us all.

“It’s important to figure out why so many of us are dying of colorectal cancer,” Harrison said. “We need to make sure what’s being researched and translated into clinical practice is not just representative of one population but multiple populations. By studying different populations, we help everybody.”

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