Untangling myeloma's racial divide

Black people are more than twice as likely to develop multiple myeloma as white people, and they are more likely to die as a result. But why? **By Cassandra Willyard**

INTERNATIONAL MYELOMA FOUNDATION

Yelak Biru is a patient advocate for people with multiple myeloma.

In 1995, Yelak Biru came down with a cough that lingered for weeks. When his wife finally forced him to see a physician, blood tests showed that Biru, then a graduate student in computer science at the University of North Texas in Denton, had severe anaemia, and more tests revealed the cause: multiple myeloma, an incurable blood cancer.

Twenty-five years later, Biru spends much of his time supporting other people with multiple myeloma. As a patient advocate, he has led myeloma support groups and participated in seminars across the United States, but he rarely sees people who look like him — people who are Black. That's striking because myeloma disproportionately affects Black people. They are two to three times more likely to develop the disease than white people. In fact, it's the most common blood cancer in people of African descent.

Although racial disparities exist for many types of cancer, they are particularly pronounced in multiple myeloma. Black people are twice as likely as white people to develop the precursor condition that can lead to full-blown disease: monoclonal gammopathy of undetermined significance (MGUS). They are also twice as likely to die of the disease. Researchers are working to better understand why these differences exist, how to mitigate them and whether early intervention might improve outcomes for Black people and at least partly remedy the imbalance. As a first step, scientists have been working to enrol more Black people in myeloma clinical trials.

Demystifying the disparity

A raft of studies have tried, with mixed success, to work out why myeloma is more common among Black people. Factors such as access to health care, obesity, alcohol and smoking, "haven't been conclusive risk factors for a doubling of the incidence", says Craig Cole, a haematologist at Michigan State University in East Lansing.

There are hints that genetic differences might have a role. For example, having close family members with myeloma is a risk factor. And one study[1] found that the prevalence of MGUS in Black men in Ghana is twice that of white men in the United States, suggesting that the disparity is linked to African ancestry.

Epidemiologist Wendy Cozen at the University of California, Irvine, has been searching for genetic risk factors for myeloma in African Americans for more than a decade. Her latest study[2] includes nearly 9,000 people without cancer and more than 1,800 Black people with multiple myeloma. Still, she and her colleagues have so far failed to find any variants that could account for the increased incidence. That could be because the sample size isn't large enough. Or perhaps the increased risk is explained by rare variants, although Cozen doesn't think that's likely. She says the higher risk of multiple myeloma and MGUS probably stems from both genetic variation and environmental and lifestyle factors.

But there's another potential explanation. Alan Goodman, an anthropologist at Hampshire College in Amherst, Massachusetts, questions the usefulness of searching for genetic explanations for racial disparities. He points out that race is primarily a social construct, and has little to do with genetics. People who share a common ancestry also share some genetic features, but self-reported race doesn't necessarily correlate with ancestry. The assumption that people of the same race share similar genetic features is an "unconscionable leap", Goodman says.

Cozen acknowledges that race is an imperfect construct, but defends the research. Researchers have found genetic variants linked to higher risk in both Black and white people. "But so far, we haven't found the explanation for the disparity in risk between the two groups," she says. "I intend to keep looking."

Better survival

Although it is unclear why Black individuals have a greater risk of developing multiple myeloma, scientists are beginning to understand why they are twice as likely to die from the disease. Black people often get diagnosed later and receive standard-of-care treatments, such as stem-cell transplants, less frequently than white people do. And an analysis of data from people who use the US federal

health-insurance programme Medicare shows that Black people tend to get access to new therapies later than white people do. "That's a huge glaring hole in terms of our health-care system that is really predicated on systemic racism," says Karen Winkfield, a radiation oncologist at Wake Forest Baptist Health in Winston-Salem, North Carolina.

When Black people do get equal access to therapies, however, they seem to fare better than white people. Nikhil Munshi, an oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts, and his colleagues sifted through the database at the US Department of Veteran's Affairs (VA) and identified 15,000 people with myeloma. Because the department offers free health care, everyone can access the same drugs. The researchers compared outcomes based on race and encountered an unexpected result. "What we found, surprisingly, but happily, was that African Americans actually had a superior overall survival," Munshi says. The median survival for African Americans was 5.1 years compared with 4.5 years for white people[3]. When they looked at individuals 65 or younger, they observed an even wider gap – a median overall survival of 7.1 years for African Americans compared with 5.8 years for white people. (In people over the age of 65, they found no significant difference in overall survival.)

Black people who are given the same treatments might fare better because they seem to develop less-aggressive forms of the disease. In one study[4], researchers sequenced the genomes of more than 800 Black people with myeloma and classified these individuals according to the percentage of African ancestry in their genome. They also sequenced participants' cancer cells to look for genetic abnormalities, including translocations – places where the chromosomes get jumbled up. Participants with 80% or more African ancestry had a greater frequency of three translocations. One, known as t(11;14), is particularly common and is typically associated with better outcomes. (The other two translocations are linked to worse outcomes, but they're rarer.)

Black people are also less likely to harbour abnormalities linked to a poor prognosis. Munshi and his colleagues looked at one particular abnormality: deletion of the short arm of chromosome 17, called 17p. That deletion is associated with negative outcomes irrespective of ethnicity, Munshi says. But the deletion is less common in Black people – just 4.7% of Black people with multiple myeloma have it, compared with 8.8% of white people with the disease[5]. "That may drive some of the better outcomes," Munshi says. He cautions, however, that 17p alone can't explain the survival advantage. There might be other mutational changes that contribute to the disparity. Munshi is also interested in exploring whether differences in the tumour microenvironment of particular ethnic groups could play a part.

Improving outcomes

One way to tackle the disparity in outcomes might be to identify and treat the disease before it takes hold. Nearly everyone who develops multiple myeloma first develops either MGUS or smouldering multiple myeloma. "Many people don't even know they have those asymptomatic precursor conditions because we don't go looking for it," says Irene Ghobrial, an oncologist who treats blood cancers at Dana-Farber. But if physicians could identify people with these precursors, pinpoint those who are likely to progress, and intervene early, they might be able to change the course of the disease, or stop its progression altogether. That would help everyone.

As a first step, Ghobrial and her colleagues plan to recruit 30,000 people with a high risk of developing myeloma – adults between the ages of 40 and 75 who either have African ancestry or a close family member diagnosed with the disease. They expect that about 3,000 of those people might harbour a precursor condition, and they will follow that cohort over time to identify biomarkers that predict disease progression.

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But not everyone sees the value of screening in multiple myeloma. "I don't think we are ready for that yet," says Sikander Ailawadhi, an oncologist at the Mayo Clinic in Jacksonville, Florida. He sees more pressing issues. "We know that African Americans are going to be disproportionately affected with myeloma because they're less likely to have access to the right treatment, they're less likely to be able to get to transplant centres, they're less likely to overcome some inherent biases that we have." Addressing those issues should be the priority, he says.

Access to new therapies before they are approved is also a problem. Black people make up 13% of the US population and 20% of people with myeloma. But an analysis by the US Food and Drug Administration (FDA) found that they represent just 4.5% of clinical trial participants[6]. That's not necessarily surprising, says Timothy Rebbeck, a cancer epidemiologist at Dana-Farber. The FDA has no authority to require that researchers include minority ethnic groups in trials. "The goal of many trials is to get a therapy approved, not necessarily to understand the diversity of the patient population," he says.

Winkfield points out that eligibility restrictions often contribute to the lack of diversity. "Oftentimes they exclude people with diabetes or heart disease," she says. "And we know, because of systemic racism, those diseases are over-represented in the Black community."

A lack of diversity in drug trials can lead to problems in the clinic. "If you limit the patients you enrol to only white males, you risk missing an important understanding of the disease, but also potentially important therapeutic options that would help everybody," Cole says.

For example, studies conducted over the past several years show that a class of drugs called BCL-2 inhibitors work much better in individuals with the common t(11;14) translocation – the genetic rearrangement often found in people with African ancestry. One such drug, venetoclax, is already approved for other blood cancers. When given alone, the drug has a response rate of 40% in people with multiple myeloma and the t(11;14) translocation, compared with 21% for all people with myeloma[7]. But according to the FDA analysis, in some clinical trials as few as 0.5% of participants were African American. "If you're one of those unfortunate places that only has an enrolment of 0.5%, you'll never get that signal," Cole says.

In February, the FDA and the American Association for Cancer Research held a joint workshop to discuss ways to increase diversity in myeloma trials. One of the most popular suggestions involved assigning clinical trials, especially late-stage trials, a diversity officer to help with enrolment. That strikes Cole as an excellent idea. "Being an African American, it has taken me a few years to understand that enrolling an African American in a clinical trial – or a Native American or a Hispanic – is very different than enrolling a white person," he says. "It takes cultural competency," he says.

A history of exploitation and mistreatment of minority ethnic groups by researchers has made many people hesitant to participate in trials. "When I talk to Black people around cancer research, they want to engage. They really want to, but there's a lot of fear", says Winkfield.

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