Genetic Causation for Mortality Disparity Among Young African American Men

Isaac Powell, MD

Karamanos Cancer Center

Overview

Clinical and genetic evidence support a faster growth rate of prostate cancer among African American compared to European American men, and even though the incidence is only about 60% higher, the death rate is 240% to 250% higher. That discrepancy is very intriguing, and we will explore that issue.

Method

We propose that a faster growth rate among African Americans compared to European Americans contributes significantly to the racial disparity of advanced disease at diagnosis and a two to three times greater mortality rate among African Americans than European Americans. We examined our autopsy series radical prostatectomy data and our SEER registry data.

The autopsy data showed that cancers actually start at the same time, and you see no difference in the prevalence of prostate cancer in the latent cancers. However, 20% of the latent cancers transform into significant cancers that would be lethal if not treated. The characteristics of the cancers are similar between African Americans and European Americans. With regard to high-grade PIN, they start at the same time with an equal distribution, but at age 40 to 49 the distribution is significantly higher among African Americans. This condition, when associated with prostate cancer, is associated with aggressive prostate cancer. Moving to the clinically significant prostate cancers, ones that were removed or where they had abnormal PSAs or abnormal digital rectal exams, you see the volume of the cancer is greater in African Americans compared to European Americans in men 40 to 69, but in men 70 to 79 European Americans had higher volumes.

Stage/Grade

Prostate cancer that is confined within the prostate is classified as stage 1 or 2. These are the curable cancers. Once it is outside of the prostate gland it is not curable, but survival may be prolonged by various treatments. In men who are diagnosed with cancer still confined in the gland, there is no difference between African Americans and European Americans and no difference in survival in men who had prostates removed. In men where the prostate was removed and the cancer was actually outside of the gland, the survival is lower for both. When the cancer is early, there is no difference, and when the cancer is confined and it is taken out, there is no difference. We see, however, in more advanced disease there is a disparity between African Americans and European Americans.

When we look at the Gleason Grade, African Americans consistently have more aggressive cancers than do European Americans, and this is responsible for the outcome that we are seeing.

Looking at cancer that had spread to other sites, primarily bone, African Americans have three times greater distal disease than European Americans.

SWOG

In men who had metastatic disease treated by hormonal therapy, we looked at African Americans and European Americans treated the same way at the same stage of disease, and African Americans had a worse outcome than did European Americans.

Contributing Factors

The impact of socio-economic status has been controversial, but I think the best studies show that it has minimal impact in terms of the disparity. Delayed diagnosis for non-financial reasons is a contributing factor. African Americans are less likely to go to the doctor, and one of the reasons that we find is they are afraid of a diagnosis. In terms of treatment differences, we know that African Americans are less likely to be treated once they are found to have prostate cancer, and they are less likely to have aggressive therapy as well. There is some difference in access to care, but the difference is not significant enough to account for the disparity that is seen.

Cancer Process

DNA is transcribed into RNA and translated into protein. Protein contributes to the tissue that we see, the normal tissue and the cancer tissue.

The DNA forms a code, and that code is established by chemicals called nucleotides. All that has to happen is the change of one chemical, one nucleotide—a single nucleotide polymorphism, to cause a change in the protein from the DNA to the RNA to the protein.

CPY3A4

CYP3A4 is a protein that is involved in the breakdown of testosterone, which is the male hormone that causes prostate cancer to progress. However, if it is inhibited, the transformation results in increased activity of testosterone. This inhibition can occur through a variant, a single nucleotide polymorphism. Studies have been done on the CYP3A4 polymorphism showing that it is associated with a higher clinical grade and stage prostate cancer, that the variant A to G allele was much more common among African Americans than European American, Hispanic or Asian Americans, and that there is a strong association between race and genotype in that 8% of European Americans and 83% of African Americans had one or more copies of the variant G allele. A follow-up study reported that aggressive disease among African American men was strongly associated with the variant allele.

8q24

Recent studies have identified multiple single nucleotide polymorphisms at 8q24 that have different racial distributions on that chromosome. It was also found that there was a greater percentage of the SNPs or variants among African Americans than European Americans, and they found that the more SNPs a man had, the more aggressive the cancer was.

Metastasis

Genes associated with invasion and metastasis demonstrated higher expression in primary tumors among African Americans compared with tumors in European Americans. Biology and genetics have a significant impact on the disease.

Conclusion

Prostate cancer that starts at the same time has no significant differences in proportions among African American men and European American men but reaches distant disease at a ratio of 3 to 1, and this supports the concept that prostate cancer is growing faster among African Americans compared to European Americans. There is growing genetic and biologic evidence to support this conclusion.

Funding

It is important to have funding for future research to continue the genetic and biological research to identify biological markers and targets for therapy for high-risk populations to eliminate the outcome disparity and to decrease the cost of healthcare by decreasing the cost of advanced prostate cancer treatment and deaths from prostate cancer, both of which are much more costly than diagnosing and treating early disease.

Questions

Participant

It seems to me that there is a lot that we don't know about prostate cancer. We try to make it very simple, to talk about it in simple terms, and that is impossible. Even when somebody gets treatment, it appears to me that in approximately 30% of the individuals the treatment fails and their disease progresses. Do we have any idea why they are failing, is there any difference between the African American population and the rest of the population, and is there anything that advocates can do to figure out the discrepancy?

Isaac Powell, MD

We know that biological factors are contributing to the men having progression of the disease. Even though they may look alike clinically and histologically, biologically they could be very different diseases. There are differences biologically and genetically in the cancers between African Americans and European Americans, and now we are beginning to study the gene/gene interactions and gene/environmental interactions. We are finding there are pathways that may be different. We are

moving toward being able to differentiate these things, and we need individuals to participate in clinical trials so that we can answer those questions.

Participant

One unmet need is some type of functional imaging to be able to actually know who has localized disease.

Isaac Powell, MD

If we could control prostate cancer like we control diabetes, I think we would be making major steps. It is not simple, and there are all kinds of things that we have to identify.

Participant

What other factors predispose African American men to have SNPs to begin with?

Isaac Powell, MD

We don't know the answer to that question.