

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Prostate Cancer in African American Men



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H&O Can you discuss the disparities between black and white American men in terms of prostate cancer incidence and death rates?

SP The good news is that the incidence and mortality rates of prostate cancer have been steadily dropping in both groups over the past 8 to 10 years. The bad news is that the disparity between black and white men has not decreased. In fact, the evidence suggests that if anything, the disparity has slightly increased. The incidence of prostate cancer is 1.6-fold higher in black men than in white men, and 2.8-fold higher in black men than in Asian men. Mortality rates are 2.4-fold higher in black men than in white men, and a 5-fold higher in black men than in Asian men.

We also know that the African American men who present to our clinics have a younger mean age at diagnosis than other groups, and a shorter mean survival. In addition, their disease is more likely to be diagnosed at an advanced stage, and they are at a greater risk for early biochemical recurrence and the development of metastases.

H&O What do we know about the causes of these disparities?

SP All health disparities, and cancer disparities in particular, are multifactorial in origin. Causative factors are as diverse as limited access to care, poverty, obesity and other comorbidities, low screening rates, delays in diagnosis, delays in treatment, differences in treatment,

and implicit bias within health systems. In some cases, overt discrimination occurs. Taken together, we think of these as social, lifestyle, and structural (health system) determinants of health. But in prostate cancer, we also know that when we control for many of these important determinants of health, a difference in both incidence and mortality persists. The difference is mitigated but not erased entirely. This finding suggests to cancer biologists and genomicists, like me, that a biological factor may also be contributing to the disparity.

H&O What could explain this biological contribution ?

SP This is a sensitive issue, and we need to be very careful in how we address it. First, we want to urge people to recognize that race in and of itself is not a biological or genetic construct. Race is a sociocultural construct. However, as a function of the human diaspora, many of the characteristics of the human species began to change as the human population proliferated and spread around the world. We don't know what the main drivers of that diversification were, but many anthropologists speculate about the contributions of diet, climate, and genetic constriction points caused by the mass extinction of different population segments. In any case, these differences—including our outward characteristics (phenotype)—have been carried forward into the modern era and are propagated across generations, which indicates that these phenotypes are encoded in our DNA (genotype). There are phenotypes

encoded in genotypes that we think of, and that can be genetically identified, as characteristic of Asian, European, Scandinavian, or African ancestry, illustrated by the current fascination with tests for genetic ancestry. In the same way that these external characteristics evolved as human populations spread around the planet, so did our internal, cellular, and molecular characteristics, including differential susceptibility to various diseases and different responses to treatment. For African Americans, in particular, we also need to recognize, appreciate, and consider the effect of the forced diaspora of the African slave trade.

So, when we talk about the biology of cancer in different races or ethnic groups, it's not a question of genetic superiority or anything like that. In fact, depending on the cancer, the disparity at the biological level can go in either direction. African Americans have a lower incidence, not a higher incidence, of multiple types of cancer.

The presence of these ancestry-related biological differences underscores how important it is to conduct medical research in diverse populations, and not to assume that the result you may get in a clinical trial that's almost exclusively composed of white patients, for example, will accurately reflect the responses you might see in a population of African, Asian, or Latinx ancestry.

H&O In clinical trials, the disparity seems to disappear or even favor black men with prostate cancer. Why would this be?

SP We have recently seen 3 extraordinary examples of this observation in studies that were stratified by race. One example is the Abi-Race trial (A Phase II Open-label, Parallel Group Study of Abiraterone Acetate Plus Prednisone in African American and Caucasian Men With Metastatic Castrate-resistant Prostate Cancer) from the Duke Cancer Institute, which Dr Daniel George, the principal investigator, presented at the 2018 annual meeting of the American Society of Clinical Oncology (ASCO). The second example is the PROCEED trial (Provenge Registry for the Observation, Collection, and Evaluation of Experience Data), which was led by Drs Celestia Higano of the University of Washington, Oliver Sartor of Tulane University, and Andrew Armstrong from Duke. This was a trial of sipuleucel-T (Provenge, Dendreon). The third is a retrospective meta-analysis of docetaxel plus prednisone that was conducted by Dr Susan Halabi from Duke. These trials evaluated hormone therapy, cellular therapy/immunotherapy, and chemotherapy, respectively. In all 3 studies, men of African ancestry entered the trial with later-stage disease but responded better to therapy than men of other ancestry. This finding is quite exciting, and we don't yet have an explanation. We have received

several grants here at Duke that are being used to explore this very question. Once again, this finding underscores the importance of conducting clinical trials with diverse populations—you never know when you're going to get a result like this.

H&O Have biological differences been identified in the prostate tumors themselves in black vs white men after stage and grade have been accounted for?

SP Numerous types of studies have found ancestry-related differences at the molecular level. First, multiple studies have sequenced DNA taken from tumors, either at biopsy or after surgery, for potential actionable mutations and have shown different proportions and different frequencies of mutation in some of the genes known to be drivers of the biology of prostate cancer. Second, molecular epidemiologists who do large-scale studies of single nucleotide polymorphisms (SNPs) have found significant differences between the SNPs of prostate tumors in men of African ancestry and those in men of European ancestry. Third, transcriptomic studies—which look at RNA—have found differences in both aggregate gene expression and alternative RNA splicing; such studies have been a focus of my own laboratory. In my previous work with Drs Norman Lee and Bi-Dar Wang at George Washington University, where I worked before I came to Duke (Dr Wang is now at the University of Maryland), we found significant and dramatic ancestry-related differences in this process of RNA splicing and in the constituent burden of alternative RNA splicing between blacks and whites. And within that very large differential burden, we found some key differentially spliced genes in which the spliced variant was a driver of the aggressiveness of prostate cancer in an ancestry-related fashion. That was a very exciting discovery that has led us toward a series of novel targets in prostate cancer. These targets may present opportunities for us to treat prostate cancer in black men differently than we might in white men, or they may lead to better treatments for prostate cancer in men of all races.

H&O Why do Asian men have a lower risk for prostate cancer and prostate cancer mortality?

SP This is an exceedingly important question, but no one has a good answer at this time. Researchers here at the Duke Cancer Institute are currently conducting studies with our collaborators in the United States, Singapore, and China that involve the collection of sequencing information on DNA and RNA. We hope that this comparative genomics approach may reveal not only why black and white men have a higher risk for prostate cancer, with

black men having the highest risk, but also why Asian men seem to have some protection against aggressive prostate cancer.

H&O What is being done nationally to reduce the outcome disparity between white and black men with prostate cancer in terms of screening, diagnosis, and treatment?

SP A lot of groups around the country, including academic cancer centers, community cancer centers, and advocacy organizations, are taking a precision approach to screening, diagnosis, and treatment. Some of the guidelines and recommendations regarding screening are based on studies done in Scandinavia, where the black population is small. By contrast, the population in Durham, North Carolina, where Duke is located, is 39.5% black. This percentage is higher than the average in the rest of the country. In response, we have created a screening algorithm here at Duke that considers our specific patient population.

To design our algorithm, we formed a prostate cancer strategy group in 2014 that continues to meet monthly. One of the first steps we took was to look at every paper ever published about screening in different populations. We factored in our own demographic data and came up with an algorithm that takes this high-risk population into consideration, and we have been testing the algorithm by integrating it into our electronic medical record (EMR). The pilot test looked at data from more than 50,000 men who underwent prostate cancer screening across nearly 40 of Duke's primary care clinics all over North Carolina. We found that this algorithm, when coupled to our EMR, produced a significant increase in guideline-concordant screening without an increase in unnecessary biopsy or treatment. A number of organizations around the country are beginning to think about similar approaches. After our algorithm was evaluated by a committee appointed by the North Carolina Advisory Committee for Cancer Coordination and Control, which included scientists and clinicians from Wake Forest Baptist Comprehensive Cancer Center and the UNC Lineberger Comprehensive Cancer Center, it was voted on and adopted as the state's screening guideline. We are very excited to see our algorithm influence statewide policy.

Regarding diagnosis and treatment, pathologists and other physicians are increasingly taking into consideration the more aggressive nature of prostate cancer in men of African ancestry when making their diagnosis and treatment recommendations.

H&O Is there anything that you'd like to add or emphasize?

SP This is an extraordinary time to be studying the science of cancer disparities. I am delighted that the American Association for Cancer Research has been so committed to this area, and that their annual Science of Cancer Health Disparities conference continues into its 12th year. It is also incredibly significant that the National Cancer Institute continues to invest heavily in cancer disparities research through its Center to Reduce Cancer Health Disparities, and that the National Institutes of Health now includes the National Institute on Minority Health and Health Disparities, which is dedicated to addressing health disparities research across many diseases.

Other large organizations, including ASCO, the American Society of Preventive Oncology, Susan G. Komen, the American Cancer Society, and the V Foundation, also are very focused on cancer disparities, with the goal of achieving cancer health equity. Likewise, a number of organizations—including the Men's Health Network, Movember, and the Prostate Cancer Foundation—are heavily focused on reversing prostate cancer disparities. It is a very exciting time to be doing this kind of research. I think it's important for us to be very purposeful and proactive, and to think carefully about how social, lifestyle, structural, and biological determinants of health interact with one another to drive cancer disparities. For example, we clearly are seeing interconnections between ancestry-related biology and neighborhood-level cancer risk factors, such as poverty, diet, smoking, and stress. We need to consider how these factors influence one another to exacerbate cancer disparities, and to find innovative ways to mitigate such disparities, at every level, to the best of our abilities.

Disclosure

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Suggested Readings

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