



ADVANCES

From the CEO

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Understanding Disparities in Prostate Cancer Incidence: A Top 10 List of Epidemiological Factors at Stake

It's *National Prostate Cancer Awareness Month*. At the Prostate Cancer Foundation (PCF), we salute President Obama for his proclamation. When it comes to reducing our nation's healthcare costs, we need to invest more resources in curing so we can spend less treating. Proclamations like President Obama's will help us build awareness and support for finding better treatments and cures for prostate cancer. We hope that next year the President "lights up" the White House "blue" as it has been lit up "pink" for breast cancer awareness. With 192,000 new U.S. cases being diagnosed this year and more than 27,000 American men expected to die from it, the burden of prostate cancer on U.S. men (the number of cases in men) is basically equivalent to that of breast cancer on U.S. women.

This summer, several folks working with the White House have asked the PCF to help explain the "state of science and public health in 2009" as it relates to prostate cancer's undue burden of death and suffering on African-American men and their families. African-American men in the U.S. have the greatest rates of developing prostate cancer on planet Earth, more than 60 times greater than men in the lowest risk countries (Japan and China). These men are 1.6 times more likely to be diagnosed with prostate cancer and 2.4 times more likely to die from it than Caucasian men. Although treatment is effective and improving for men with localized prostate cancer, African-American men more often present at an advanced stage. Prevention holds the greatest promise to reduce suffering from prostate cancer in the long run.

In a perfect world, with absolute *equal access to equal care*, African-American men experience a greater burden of prostate death and suffering due to epidemiological differences we do not yet fully understand. We do not live in a perfect world. The former NCI Director Dr. Samuel Broder once said, "poverty is a carcinogen." The same may be said about many "cancer disparities" as defined by the American Cancer Society. Inequalities in access to care substantially affect the burden of prostate cancer in men.

Mindful that one can not fully disengage the impact of poverty from most factors to be considered, this *Advances* seeks to address defined inequalities with fundamental new

research ideas on environment, diet, genes, and human behaviors that cause the 60 times greater incidence of prostate cancer in African-American men compared to men in Asia. Dr. Lorelei Mucci at the Harvard School of Public Health, one of the world's leading and most thoughtful prostate cancer experts, worked with me and the PCF to summarize a Letterman-style "Top 10 list" of epidemiological factors that need to be solved to reduce the undue burden of death and suffering from this disease in African-American men and their families.

The Top 10 List

The 10 factors that we have selected are based on their known or suspected role in the development or progression of prostate cancer. We discuss the state of science on these topics, the potential variability in frequency of the factors among African-American men, and summarize potential future directions to take with these areas of research in order to identify the underpinnings of disparities and find opportunities for prevention.

- 10) **Obesity.** There is growing data, including from our group (Ma, 2008), that men who are overweight or obese are more likely to develop advanced stage prostate cancer. Moreover, among men with prostate cancer, those who are overweight prior to diagnosis are at increased risk of cancer-specific mortality. In the U.S., the rates of obesity based on national statistics are similarly high among Caucasian and African-American men. Thus, while the link between obesity and prostate cancer progression is important as a public health issue, it is unlikely that obesity per se explains the high prostate cancer rates among African-American men.
- 9) **Stress.** There are scant data evaluating the potential role of acute and chronic stress, due to stressful situations or psychological stress, on prostate cancer incidence or mortality. However, while the effects of acute stress on human health, including cardiovascular disease, have been well documented, there is stronger evidence linking stressful events and the risk of breast cancer (Nielsen, 2005). Whether higher exposure to acute and chronic stress could explain racial disparities in prostate cancer should be an expanded area of research.
- 8) **Testosterone and other sex hormones.** Sex hormones, including testosterone, clearly contribute to the growth and progression of prostate cancer, although there is still debate around the importance of circulating levels of specific hormones or genetic markers in these pathways in prostate cancer. The frequencies of some genetic factors, as well as the levels of specific sex hormones, do differ by race and ethnicity. Thus, it is plausible that that racial variation in sex hormones may account in part for differences in rates of prostate cancer.
- 7) **Insulin.** High levels of circulating insulin in the blood can occur as a result of obesity as well as uncontrolled diabetes. The consequences of hyperinsulinemia include raised triglyceride levels and hypertension. The one study to date that examined insulin levels measured prior to cancer diagnosis found that hyperinsulinemia was linked with both prostate cancer risk and progression. Although rates of obesity do not differ, African-American men have higher rates of uncontrolled diabetes and hypertension than Caucasian men. High insulin could potentially contribute to the

higher risk of prostate cancer incidence and mortality in African-American men. Controlling insulin levels is achievable through therapeutic or lifestyle interventions.

- 6) **Coffee.** Coffee has potent antioxidant capacity, lowers circulating markers of inflammation, improves glucose control and has been linked with a lower risk of diabetes (Van Dam, 2005). Although coffee intake and total prostate cancer incidence has been studied in a few settings, no published study has examined coffee and prostate cancer progression. In our preliminary analyses within two cohorts of men based in the U.S. and Sweden, men who drank the highest amounts of coffee (3 or more servings per day) were 60 percent less likely to develop fatal prostate cancer compared to those who drank no coffee. Although these two populations were primarily comprised of Caucasian men, the finding is intriguing, since coffee intake is considerably lower among African-American men in the U.S. (Storey, 2006). This novel finding must be confirmed in additional settings, and should be tested among a population of African-American men.
- 5) **Genetic susceptibility.** The Human Genome Project has led to rapid identification of specific variants in our germline DNA that increase risk of cancer, including prostate cancer. Multiple studies (e.g. Schumacher et al, 2007) have now confirmed that specific markers in an area of the genome known as 8q24 affect risk of prostate cancer. Interestingly, one of the initial studies that identified 8q24 did so through identifying genes that are associated with African-ancestry (Freedman M, 2004). The frequency of the 8q24 alleles is higher in African-American men compared to those of European ancestry, suggesting genetic susceptibility may explain part of the disparity in incidence rates. Research on specific genetic markers and prostate cancer mortality is currently limited, making it an area of considerable importance for addressing racial disparities in prostate cancer.
- 4) **Lycopene/Tomatoes.** Tomatoes are rich in lycopene, a carotenoid with well-documented antioxidant effects, which may lower prostate cancer risk—particularly advanced disease. A thorough summary of epidemiological findings on tomatoes and prostate cancer risk suggest that men with the highest intake of tomatoes have a 20-30 percent lower risk of developing prostate cancer (Etminan, 2004). The association between tomatoes and lycopene is stronger for preventing advanced stage disease. Intake of tomato products, particularly cooked tomatoes, is generally lower in African-American men compared to European men, particularly those of Mediterranean heritage (Allen, 2009). Whether the protective effect of tomatoes is due to lycopene or other components of tomatoes still needs to be explored.
- 3) **Insulin-like Growth Factor 1 (IGF-1).** A promising advance in our understanding of prostate cancer involves the hormone IGF-1, which plays a role in the growth of both normal and tumor cells. There is convincing evidence that men who have high levels of IGF-1 are 50 percent more likely to develop prostate cancer in the future compared to those with low levels; the relation between IGF-1 and development of an advanced stage prostate cancer is even stronger (Chan, 2002). Although overall levels of IGF-1 in circulation are similar among African-American and Caucasian men, some studies suggest that the ratio of IGF-1 to its Binding Protein 3 (which would affect the bioavailability of IGF-1 to exert its effects on tumor cells) is lower in

African-American men (Platz E, 1999). This area of research needs further exploration. Lifestyle and dietary factors (milk consumption, body size, height) are linked with levels of IGF-1, suggesting that even levels of a growth factor are modifiable, holding promise for prevention.

- 2) **Vitamin D.** Vitamin D deficiency is an emerging public health problem, which looms particularly large for African-American men. A recent study suggested that African-American men at risk for vitamin D deficiency had a 60 percent greater risk of cancer overall, and a 220 percent greater risk of cancer mortality than Caucasian men. However, there was no difference in cancer risk or mortality among African-American men who were not at risk of vitamin D deficiency (Giovannucci, 2006). Although epidemiological studies generally have not found an association for vitamin D status and prostate cancer risk overall (Mucci, 2008), there is tantalizing evidence to suggest vitamin D deficiency may predispose a man to develop an aggressive form of prostate cancer. Given the large differences in vitamin D status among African-American men, the vitamin D hypothesis for prostate cancer merits further study.
- 1) **Infectious diseases.** Two recent studies from our group at Harvard suggest that men who have ever been infected with *Trichomonas vaginalis*, the most common non-viral sexually transmitted infection, are more than twice as likely to develop an aggressive prostate cancer (Sutcliffe S 2008, Stark JR 2009). The hypothesis is that common infections can ascend to the prostate, leading to chronic inflammation and eventually to cancer. The prevalence of sexually transmitted infections, including *T vaginalis*, tends to be high among African-American men, which could contribute to some variability in prostate cancer mortality. The hypothesis around infections and prostate cancer mortality is currently being investigated in a cohort of men who are primarily African-American. STIs such as *T vaginalis* are easily diagnosed, and there are inexpensive and effective treatments, offering the potential for prevention.

One of the major barriers to identifying the disparity of prostate cancer among African-American men has been the lack of epidemiological studies with inclusion of sufficient numbers of men across different races. We may also gain insight by studying the demographic shift and related increase rates of prostate cancer seen in parts of Africa.

“This month, we remember the lives we have lost, and we recommit ourselves to supporting those currently battling against the disease,” declared President Obama in his proclamation. PCF is working daily with scientists and research partners to reduce the burden of prostate cancer in all men, and to make strides especially for those who face undue burdens. With what Martin Luther King, Jr. called the “fierce urgency of now,” the PCF persists in our dream of a world without death and suffering from prostate cancer as we work with partners, scientists, patients and families to find answers to the questions raised by our Top Ten list of research ideas for epidemiology related to African-American men and prostate cancer.

For more on Dr. Mucci and other PCF-funded investigators, please visit www.pcf.org.
