Why Do African-American Men Suffer More Prostate Cancer?

For decades, African-American men have had the highest prostate cancer incidence rate of any racial/ethnic group in the world. At 261.9 new cases per 100,000 in 1993, their rate is two-thirds higher than whites and more than twice as high as rates for Asian-Americans.

Researchers have yet to find a definitive reason for these lopsided incidence rates. But their data suggest that diet, genes, and hormones all play a part. Migrant studies, particularly of Asians, show that prostate cancer risk increases when people migrate to the United States, just as it does for many other cancers. These findings, said Alice Whittemore, Ph.D., of the Stanford University School of Medicine, Calif., are the strongest to date showing that an environmental factor — diet, lifestyle or something else — is involved in the development of prostate cancer.

Data on cancer rates in Africa are sparse, allowing little or no comparison between Africans and African-Americans.

Environmental factors have so far been able to account for only a fraction of the difference in incidence rates among blacks, whites, and Asians. Prostate cancer is one of the few major cancers where the epidemiologic evidence indicates the involvement of genetic factors, said Walter Willett, M.D., Dr. P.H., of the Harvard School of Public Health, Boston. “The epidemiology really does suggest that there is something more than just diet and lifestyle.”

Most theories on the origins of prostate cancer are based on the idea that male hormones, or androgens, are involved — in particular, testosterone and its metabolic product dihydrotestosterone. In the prostate, dihydrotestosterone is the principal factor driving cell proliferation, the common denominator in most, if not all, cancers, experts said. They note that huge amounts of androgens are required to induce prostate cancer in virtually all animal models of the disease. And in humans, the mainstay of therapy for metastatic disease is androgen ablation, removing the source of androgen by surgery or drug therapy, to which 80% to 90% of patients respond initially.

The evidence implies that cumulative exposure to androgen may be important in the development of prostate cancer, suggesting that the higher incidence rates among blacks may result from larger or longer exposures to it. Much of the current research is looking for genetic and environmental factors that act or interact to alter androgen exposure over a man’s lifetime.

“The assumption is that diet, if it is an important risk factor, is acting through some hormonal pathway . . . and maybe that hormonal pathway has some genetic components to it that can vary across populations,” explained Laurence Kolonel, M.D., Ph.D., of the Cancer Research Center of Hawaii in Honolulu. “So [blacks] may be more genetically predisposed to get prostate cancer if they’re in a particular environment.”

Testosterone Exposure

African-American men may be exposed to higher levels of testosterone, literally from the start, because of diet-related hormonal influences, according to Ronald K. Ross, M.D., of the University of Southern California/Norris Comprehensive Cancer Center in Los Angeles. In a study of early pregnancy, Ross found that testosterone levels were 50% higher in African-American women than in white women. He speculates that this increased hormonal exposure in utero might reset the so-called “gonadostat feed-back loop,” which regulates testosterone secretion, to a higher level.

A follow-up study of healthy young men found that circulating testosterone levels were 15% higher in African-Americans than in whites, Ross said. The difference may not seem large. But considering that prostate cancer incidence increases rapidly with age, a sustained, increased testosterone exposure of 15% could explain a 70% or 80%
higher rate of prostate cancer in blacks, he said.

In extending the follow-up to young men in Japan, Ross found to his surprise that their testosterone levels were similar to those of U.S. whites. But the study also suggested that the Japanese had lower activity of 5-alpha reductase than did U.S. whites and blacks. This enzyme metabolizes testosterone into dihydrotestosterone, or DHT, which is at least eight to 10 times more potent than testosterone (see sidebar). This finding, Ross said, is "very consistent with the role of androgens in prostate carcinogenesis and in explaining the racial/ethnic variations in risk."

The 5-alpha reductase type II gene is one of several that Ross’s group is investigating for possible effects on testosterone secretion and metabolism and other androgen activity. He said they have found some forms of this gene that are unique to African-Americans and a few that are unique to Asian-Americans as well.

**Androgen Receptor**

Differences in prostate cancer incidence among blacks, whites, and Asian-Americans might also be influenced by variations in androgen receptor, the protein that moves androgens around in prostate cells. The AR gene is polymorphic, having a particular sequence of bases that is repeated from eight to 30 times in different individuals.

Evidence from several research groups suggests that longer repeat lengths are associated with lower AR activity, while shorter repeat lengths are related to greater AR activity. In addition, the frequency of particular repeat lengths has been found to vary significantly among racial/ethnic groups. A study found that the most common repeat length was 17 in African-Americans, 21 in whites, and 22 in Asian-Americans.

"The hypothesis is that men with short repeat lengths in their androgen receptor gene will be more susceptible to prostate cancer — perhaps at an early age, although we have no evidence for that yet. And perhaps they will develop a prostate cancer that’s more aggressive," said Evelyn Barrack, Ph.D., of the Johns Hopkins School of Medicine in Baltimore. "That might account for a higher frequency of prostate cancer in African Americans."

**Dietary Factors**

Among environmental factors, diet — especially fat — seems the most likely to play a role in the ethnic variations in prostate cancer incidence, scientists said.

In a study headed by Whitemore, researchers found a positive association between fat intake and prostate cancer risk in blacks, whites, and Asian-Americans (see Journal, May 3, 1995). The data showed that African-Americans on average consumed more calories than whites or Asian-Americans and that a higher percentage of those calories came from fat. Nevertheless, these differences were large enough to explain only about 10% of the difference in incidence rates between blacks and whites.

"My prejudice after studying this is that there must be some form of genetic differences, possibly also gene-environment interactions," Whitemore said. "It could well be that dietary fat intake is playing a role in this, too. But dietary fat intake by themselves are not enough to explain an appreciable fraction of the differences."

— Hugh McIntosh

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**PCPT Completes Enrollment: 18,000 Men on Study**

Enrollment into the Prostate Cancer Prevention Trial was completed Dec. 6, 1996, with more than 18,000 men participating at 224 sites around the country. Half of the subjects are receiving finasteride, a 5-alpha reductase inhibitor, and half a placebo, according to study director Ian Thompson, M.D., of Brooke Army Medical Center in San Antonio.

The 5-alpha reductase activates testosterone into a much more potent form — dihydrotestosterone, or DHT, he said. By blocking 5-alpha reductase activity, finasteride (Proscar) lowers the DHT level significantly, and presumably decreases the cumulative exposure of the prostate to the potentially carcinogenic androgen.

"If you can reduce the cumulative androgen exposure to the prostate, perhaps you may delay or prevent prostate cancer," Thompson said. The trial will last 7 years, he said, and preliminary results could be available in the year 2004.

— Hugh McIntosh

Dr. Ian Thompson