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AFRICAN AMERICAN MEN AND HEREDITARY/FAMILIAL PROSTATE CANCER: INTERMEDIATE-RISK POPULATIONS FOR CHEMOPREVENTION TRIALS

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ABSTRACT

The risk of prostate cancer diagnosis among African Americans is 66% greater than among European American men. For African Americans with a family history of hereditary prostate cancer the increased risk of diagnosis is even greater. Thus, this population should be a prime target for chemoprevention strategies. In addition to the higher incidence of prostate cancer among African Americans compared with other populations, the mortality of prostate cancer among this high-risk population is significantly greater than 100% compared with other populations, thus further demonstrating the need for chemoprevention in this target population. Autopsy studies and clinical findings support the argument that prostate cancer exhibits more aggressive biological behavior and perhaps more rapid growth among African Americans compared with European Americans. It is hypothesized that genetic and epigenetic factors may be responsible for a more rapid growth rate among African Americans compared with other populations. Accumulating evidence indicates that a diet high in fat content is closely associated with prostate cancer progression. Investigators have reported that fat intake and percentage of energy from fat were highest in African Americans, followed by European Americans, Japanese Americans, and Chinese Americans. In conclusion, African Americans are an important target population to include in chemoprevention trials that include dietary factors as preventive agents. *UROLOGY* **57** (Suppl 4A): 178–181, 2001. © 2001, Elsevier Science Inc.

Risk factors for the development or progression of prostate cancer have been examined in many studies and include racial and ethnic background, family history, dietary history, occupation, alcohol consumption, benign prostatic hyperplasia, and hormones. The focus of this report will be the contribution of racial and familial background to prostate cancer risk and outcome and the impact of these factors on chemoprevention strategies.

ROLE OF RACIAL AND ETHNIC BACKGROUND

The reported incidence of prostate cancer between different racial and ethnic groups varies

greatly. Many studies have reported that African-American men have higher rates of prostate cancer than do European American men, and that Asian American men have very low incidence rates. This has been attributed to environmental factors, such as diet, screening, and biologic factors. When compared with their white counterparts, black men have a greater tendency to present at a younger age and later stage of disease. In 1993, the incidence rate for African American men also increased, whereas the incidence rate for European American men decreased.¹

It is well known that the incidence of prostate cancer is greater among African Americans than European Americans—66%.^{2–4} More important and perplexing is the disproportionate difference in mortality, which is two to three times greater (approximately 150%) among African Americans compared with European Americans under age 70 years. The disparity of percentages between mortality and incidence when comparing these populations is equally confusing. Possible explanations for these findings have been discussed in the literature. Prostate cancer is diagnosed at more ad-

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vanced stages among African Americans compared with European Americans.⁵ Delayed diagnosis resulting from nonfinancial barriers (eg, fear of prostate cancer diagnosis) has been demonstrated.⁶ However, the question remains, Does prostate cancer grow at a faster rate among African Americans compared with European Americans? At a time when chemoprevention and cancer control strategies are being developed, it is most important to explore biological questions that may answer the above question and that may provide targets for chemoprevention and cancer control among the high-risk population of “young” African Americans (between ages 40 and 70 years).

RATIONALE FOR THE BIOLOGICAL BASIS FOR A WORSE PROSTATE CANCER OUTCOME AMONG AFRICAN AMERICANS VERSUS EUROPEAN AMERICANS

Autopsy studies have shown no statistical difference between the two ethnic groups in prevalence and initiation of prostate cancer. Between the ages of 20 and 29 years, 8% of African Americans and European Americans develop focal latent prostate cancer.⁷ However, the examination of high-grade prostatic intraepithelial neoplasia (HGPIN) in autopsy specimens demonstrated a greater prevalence among younger African Americans than European Americans beginning in the decade of 40 to 49 years of age. The presence of HGPIN is closely associated with clinically aggressive prostate cancer.⁸ It is known that HGPIN is dependent on androgen activity. Another autopsy study showed a higher volume of prostate cancer among African Americans compared with European Americans between the ages of 40 to 49 years who have died of other causes.⁹ This suggests a greater cell proliferation owing to possible upregulated cell cycle and/or downregulated apoptosis among African Americans versus European Americans.

When we examined clinical findings, there appeared to be more evidence for a more progressive prostate cancer among African Americans compared with European Americans. In data examined at Wayne State University, Karmanos Cancer Institute, Detroit, Michigan, from radical prostatectomy specimens from men with clinically localized prostate cancer, African Americans had a higher percentage of lesions diagnosed with Gleason scores of 8 to 10 compared with European Americans.^{10,11} These differences were particularly evident among younger patients.¹⁰ Land *et al.*¹² reported that African Americans had a higher percentage of prostate cancer (Gleason score of 8 to 10). These findings support the argument that prostate cancer exhibits more aggressive biological behavior and perhaps more rapid growth among

African Americans compared with European Americans.

We examined prostate cancer specimens from radical prostatectomy stage, and found that African Americans and European Americans diagnosed with organ-confined prostate cancer demonstrated similar prostate-specific antigen (PSA), Gleason grade, and biochemical recurrence. However, men diagnosed with nonorgan confined disease demonstrated higher PSA and greater recurrence among African Americans versus European Americans. There was a trend of African Americans having a greater proportion of high-grade lesions than European Americans when prostate cancer was not organ confined. It is hypothesized that African Americans have a more rapid growth rate of prostate cancer responsible for these clinical findings that is genetically and epigenetically based.¹¹

POSSIBLE BIOLOGICAL TARGETS FOR PROSTATE CANCER PREVENTION AND CONTROL

Diet or other epigenetic factors may play an important role in explaining the ethnic differences of prostate cancer outcome. Accumulating evidence indicates that a diet high in fat content is closely associated with prostate cancer progression.¹³ Whittemore *et al.*¹⁴ studied prostate cancer in relation to diet among US citizens and Canadians of African, European, and Asian descent. Fat intake and percentage of energy from fat differed appreciably among different ethnicities; they were highest in those of African descent followed by those of European, Japanese, and Chinese ancestry.¹⁴ It has been shown that 12 (S)-hydroxy-eicosatetraenoic acid (12 [S]-HETE), the metabolite of arachidonic acid (a free fatty acid), enhances the invasiveness and metastatic potential of prostate cancer. The enzyme responsible for 12 (S)-HETE biosynthesis is 12-lipoxygenase. Preliminary data examining the correlation of race, age, stage, and 12-lipoxygenase on RNA expression indicate a greater percentage of elevated 12-lipoxygenase expressions among African Americans versus European Americans. However, the sample size was small and the difference was not significant.¹⁵

Giovannucci *et al.*¹⁶ reported that intake of lycopene or other compounds in tomato-based foods appeared to reduce prostate cancer risk. These researchers further demonstrated that African Americans consumed tomato-based products infrequently, and their serum lycopene intake was lowest of all ethnic groups studied. Other dietary targets, such as vitamin E and selenium and dietary/hormonal targets such as vitamin D, which could be the focus of chemoprevention or cancer

control among African Americans, have not been adequately studied.

Prostate cell division is controlled by testosterone after intracellular conversion to its reduced form, dehydrotestosterone, by 5- α -reductase. It has been demonstrated that shorter CAG repeat length is associated with increased androgen stimulation and the diagnosis of prostate cancer at a younger age.¹⁷ It also has been reported that African Americans have a greater percentage of short CAG repeats on the androgen receptor gene than European Americans.¹⁸ Blockage of expression of the CAG loci on the androgen receptor gene among men at risk for prostate cancer progression may be an effective means of prostate cancer intervention and control.

EVIDENCE FOR HEREDITARY/FAMILIAL INVOLVEMENT IN PREDISPOSITION TO RISK FOR PROSTATE CANCER

FAMILY HISTORY OF PROSTATE CANCER

In a population-based, case-control study of 563 cases and 703 controls by Lesko *et al.*,¹⁹ the results indicate that there is increased risk if prostate cancer is reported in either the father or the brother, and the risk increases if there are multiple relatives affected. Lesko *et al.* also found an inverse relation between the subject's age and the age at diagnosis of prostate cancer in the affected relative. For probands younger than age 60 the odds ratio (OR) was 5.3, for those 60 to 64 years of age the OR was 2.7, and for those over 65 the OR was 1.6. In a large case-control study of more than 1500 cases and 1600 controls, three racial/ethnic groups (whites, blacks, and Asians) in the United States and Canada were studied.¹⁴ This study showed that men having a history of prostate cancer in first-degree relatives have a statistically significant two- to threefold increase in risk, and the risk was shown to be similar in the three racial/ethnic groups. In this study, men who with both a brother and a father and/or son affected with prostate cancer, relative risk was estimated to be 6.4. Increased risk in men with affected relatives has been shown in a number of other studies.²⁰⁻²⁴ Although family history risk was not associated with an earlier age at diagnosis in a study conducted in Canada,²³ risk due to family history has been shown in many studies to be related to age of onset of affected relatives.^{22,25}

Among male relatives of breast cancer patients, an increased risk of prostate cancer was described by Thiessen.²⁶ Several investigators have reported on the clustering of breast and prostate cancer in families.^{27,28} However, in the study by Isaacs in families selected because of the presence of prostate cancer, there was no association between pros-

tate cancer and other cancers.²⁹ Finally, it has been reported that a high percentage of men diagnosed with prostate cancer at young age (less than 55 years old) may have hereditary prostate cancer. There is an ongoing search for a hereditary gene(s), and there are two possible candidates on chromosome 1 and one on chromosome X.^{30,31}

A segregation analysis suggested that an autosomal dominant germline mutation may be responsible for a significant portion of early-onset prostate cancer.^{22,30} Using this model, it is estimated that approximately 0.6% of white men in the United States are carriers of a prostate cancer susceptibility gene. The lifetime risk of disease in carriers is estimated to be 88% compared with a risk of 55% in noncarriers. A genomewide scan was performed in 66 high-risk prostate cancer families from North America and Sweden with evidence of linkage to the long arm of chromosome 1 (1q24-25). An additional 25 families were studied, with strong evidence of linkage in the 91 families.^{21,30} Loss of heterozygosity studies had not shown genetic alterations in the chromosomal region 1q24-25. Early results demonstrate greater prevalence of alteration on chromosome 1q24-25 among African Americans compared with European Americans, but a greater prevalence of alteration on chromosome X-q28 among European Americans than African Americans (personal communication).

Using loss of heterozygosity (LOH), several studies have consistently identified chromosomal deletions in potential tumor suppressor genes on chromosomes 3p, 6q, 8p, 10q, 13q, 16q, and 18q. Indeed, 8p22 deletions have been identified in almost 70% of patients with prostate cancer.²⁹⁻³⁵

STUDIES UNDERWAY

Two studies are currently being performed. The first study is recruiting African American families to further substantiate chromosomal findings. Thus far, 46 families have been recruited into this investigation. The average number of men diagnosed with prostate cancer per family is 5.1. Genotyping of these families is incomplete. The outcome of these genetic studies may provide targets to block gene expression and prevent forms of hereditary prostate cancer.

The second investigation involves a detailed study of first-degree male relatives of young prostate cancer probands. Included among the more important questions asked are the following:

- What is the frequency of chromosome 1q abnormalities in early-age-of-onset familial prostate cancer? Does LOH of other sites occur? With what frequency?
- What is the biological status of the at-risk cohort? Is PSA or PSA density elevated? Are chromo-

somal abnormalities present? Is polyamine content elevated (or not)? Are surrogate endpoint biomarkers of progression and invasion evident? Is prostatic intraepithelial neoplasia (PIN) present?

- What is the risk factor profile in the probands—early onset prostate cancer? Is the risk factor profile of the at-risk cohort different from that of probands? How does the profile(s) correspond/relate to surrogate endpoint biomarkers/PIN?

- Can difluoromethylornithine alter PSA density, surrogate endpoint biomarkers, or PIN in the at-risk cohort?

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