The underlying biology of carcinogenesis should be addressed in African American men at high risk for prostate cancer.

Chemoprevention in African American Men With Prostate Cancer

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Background: Recommendations for cancer screening are uncertain for the early detection or prevention of prostate cancer in African American men. Thus, chemoprevention strategies are needed to specifically target African American men.

Methods: The evidence was examined on the biological etiology of disparities in African Americans related to prostate cancer. Possible chemopreventive agents and biomarkers critical to prostate cancer in African American men were also studied.

Results: High-grade prostatic intraepithelial neoplasia may be more prevalent in African American men, even after controlling for age, prostate-specific antigen (PSA) level, abnormal results on digital rectal examination, and prostate volume. Prostate cancer in African American men can lead to the overexpression of signaling receptors that may mediate increased proliferation, angiogenesis, and decreased apoptosis. Use of chemopreventive agents may be useful for select populations of men.

Conclusions: Green tea catechins are able to target multiple pathways to address the underlying biology of prostate carcinogenesis in African American men, so they may be ideal as a chemoprevention agent in these men diagnosed with high-grade prostatic intraepithelial neoplasia.

Introduction

Despite treatment advances in recent years, prostate cancer remains the leading cause of cancer-related death among men in the United States. In 2016, the American Cancer Society estimates that 180,890 new cases of prostate cancer will be diagnosed in the United States, and 26,120 men will die from the disease. Racial and geographical differences have been observed, including a 40-fold difference in incidence rates between low-risk (Chinese men) and high-risk populations (African American men). In the United States, age-standardized incidence rates for prostate cancer are 272 per 100,000 men for African Americans compared with 164 per 100,000 men for whites. Compared with white men, African American men with...
prostate cancer have more aggressive disease, higher rates of incidence, are diagnosed at a younger age, present with more advanced disease at diagnosis, and have a worse prognosis. The mortality rate for African American men with prostate cancer is 3 times higher than white men, although the rate decreased in both groups between 1990 and 2000.

With disparate rates of prostate cancer as well as aggressive prostate cancer observed in African American men, the logical approach is to focus efforts on prostate cancer screening for early detection and prevention. However, uncertainties still exist about the overall value of early detection. Although periodic testing for serum concentrations of prostate-specific antigen (PSA) may reduce the mortality of prostate cancer, PSA testing has been linked to increased diagnoses and overtreatment of clinically insignificant, potentially indolent tumors that pose little risk of metastasis or death. Taking the accumulated evidence into consideration, the US Preventive Services Task Force recommended against PSA-based prostate cancer screening in asymptomatic men. However, these recommendations note that, in African American men, firm conclusions cannot be made to balance the risks and benefits of such screening because data do not exist to support a more favorable risk–benefit ratio. Two cancer screening trials included a majority of men with European ancestry, thus largely precluding conclusions specifically pertaining to men of African descent. Hence, no specific evidence-based recommendation regarding prostate cancer screening exists for the high risk population of African American men, underscoring the need for chemoprevention strategies targeting African American men.

**Biological Etiology of Disparity**

The etiology of increased susceptibility of African American men to prostate cancer has not been elucidated, but it is likely multifactorial involving genetic, biological, sociocultural, and lifestyle determinants. The initiation and progression of prostate cancer involves a complex series of events. During progression, genetic changes and loss of cellular control are observed as cell phenotypes change from normal to dysplasia (prostatic intraepithelial neoplasia), severe dysplasia (high-grade prostatic intraepithelial neoplasia [HGPIN]), clinically localized disease, and to metastatic disease. Observations point to the role of genetic susceptibility factors in human prostate cancer. Other than older age, African ancestry and family history of prostate cancer are well-established, nonmodifiable risk factors for prostate cancer. The lifetime risk of prostate cancer increases 1.5- to 4-fold in men with 1 or 2 first-degree relatives with prostate cancer. A Scandinavian study of twins estimated that 42% of the observed rate of prostate cancer susceptibility was associated with inherited genetic risk factors.

Genetic risk factors are also significant at a younger age, and the attributed risk of inherited susceptibility is thought to be as high as 40% among men diagnosed with prostate cancer at 55 years or younger. Although genome-wide association studies (GWASs) and large genetic variation studies have identified more than 100 prostate cancer risk loci, elucidating the biological basis for these associations is challenging. Identified risk loci include the noncoding variants, such as those located in the 8q24 region, as well as polymorphisms in the gene-coding regions that either alter, or are predicted to alter, protein expression (eg, HNF1B, TERT, RNASEL, KLK3).

**HNF1B** single-nucleotide polymorphisms (rs7501939 and rs4430796) have been identified in GWASs of prostate cancer and are associated with a risk of prostate cancer in African American men. In addition, the *CTBP2* single-nucleotide polymorphism rs4962416 is associated with risk of prostate cancer in white men. *HNF1B* encodes a transcription factor protein that forms heterodimers with other members of the *HNF1* family and can influence the gene transcription. While it was previously believed that *HNF1B* expression is specific to the liver, its transcripts have been identified in various tissues, including bone marrow, and the pancreas, urinary tract, gastrointestinal organs, and prostate. Mutations in *HNF1B* cause type 5 maturity-onset diabetes that may be accompanied by urinary tract disorders. Some men with *HNF1B* mutations have malformations in the reproductive tract, including epididymal cysts, agenesis of the vas deferens, or infertility due to abnormal spermatogenesis.

Post-GWASs are suggestive of the interaction between genetic variants and environmental risk factors, but our understanding of this is still inadequate. Rs7501939 at *HNF1B* has been shown to increase the risk of prostate cancer in African American men who are obese but not in African American men who are not obese or European American men of any body weight. Although these are preliminary findings, they suggest that weight-loss interventions may decrease the risk of prostate cancer in African American men who are carriers of the high-risk allele at rs7501939 of *HNF1B*. Future studies should further examine this observation.

*CTBP2* encodes a transcriptional co-repressor activated under stress and can mediate the stress-induced migration of tumor cells. *CTBP2* expression is detected in the prostate and has been linked to decreased *PTEN* expression and activation of the phosphatidylinositol 3-kinase pathway, which may support or promote the growth of prostate cancer.

Lindquist et al reported a higher prevalence rate of mutations in *MUC3A* and *PRIM2* in African American men with prostate cancer when compared with
their white counterparts. MUC3 is involved in cell signaling, growth, and survival; MUC3 and PRIM2 are also associated with carcinogenesis. The different patterns of somatic mutations observed between racial groups may help provide a basis for understanding the genomic contributions to aggressive tumors and associated disparate outcomes in African American men with prostate cancer.

Evidence is also emerging for racial differences in markers of prostate tumor subtypes. For example, gene fusions in TMPRSS2 and ERG are found in prostate tumors. However, several studies report that the prevalence of TMPRSS2–ERG fusions in the tumors of African American men is lower than that observed in white men. Thus, future studies must continue to pursue this research because such racial differences in marker expression could reveal mechanisms contributing to race disparities.

Differences exist in tumor biology between African American men and white men and may be attributable to race-specific differences in tumor location (ie, anterior vs posterior tumors). African Americans have an increased incidence of prostate cancer (located anterior to the peripheral zone in radical prostatectomy specimens) that may potentially have a prognostic significance. In a study of 1,245 patients who underwent radical prostatectomy, the overall tumor locations were anterior in 14%, posterior in 58%, or both in 28% of cases. The incidence of anterior tumors was higher in African American men compared with white men, and the rates of positive surgical margins in anteriorly and posteriorly located tumors were 60% vs 38% in African American men and 48% vs 27% in white men, respectively.

In patients with an abnormal level of serum PSA and negative findings on sextant prostate biopsies, biopsy is recommended for the anterior zone of the prostate. In a study of 398 men, of whom 70% were African American men, most patients had prostate cancer limited to the peripheral zone or in both the peripheral and anterior to the peripheral zone. For 4% of study patients, prostate cancer was limited to the anterior to the peripheral zone — 5% of African Americans vs 2% of those not of African American descent — but this result was not statistically significant. Another study showed a biologically important relationship between tumor location and molecular subtype, but racial differences in molecular subtypes did not persist when tumors were analyzed by location. The study investigated triple-negative disease and AR signaling. African American men were more likely to be positive for m-SPINK1 and have triple-negative disease than white men.

Based on this evidence, the racial differences in location of the prostate cancer do not appear to be significant, nor are they likely to impact the prognosis and management of prostate cancer in African American men.

HGPIN is considered by many to be a premalignant lesion of prostate cancer. Data from some studies suggest that the prevalence of HGPIN is greater in African American men and that subgroups of African American men with HGPIN are more prone to the development of aggressive, clinically significant cancer. HGPIN may also be a risk factor for biochemical recurrence following definitive treatment in African American men. HGPIN is more prevalent in African American men, even after controlling for age, PSA level, abnormal findings on digital rectal examination, and prostate volume. Significantly higher prevalence rates of HGPIN have been reported in African American men aged 40 to 49 years compared with white men (46% vs 29%, respectively), suggesting that this early-onset age range may represent the beginning of a racial disparity related to prostate cancer; this is because more African American men with HGPIN go on to develop prostate cancer. In concordance with these data, Potts et al reported that African American men were more likely to be diagnosed with prostatic intraepithelial neoplasia compared with white men, even after adjusting for PSA levels.

In a study to investigate racial differences in tumor burden (cancer volume, cancer percentage, and tumor volume–PSA ratio) in a large cohort of men undergoing radical prostatectomy, African Americans had higher disease burden (estimated tumor volume, percent of cancer involvement, estimated tumor volume–PSA ratio) compared with non–African American men. This association was pronounced in low-grade cancer (Gleason score ≤ 6), thus depicting a complex picture of relations between race and tumor burden across the aggressive spectrum of prostate cancer. The frequency of HGPIN and the autopsy prevalence of prostate cancer have been reported to be similar in large studies comparing Asian and Western populations, with widely differing incidence and mortality rates, suggesting an environmental influence on the expression of this disease and the possibility of preventing disease progression from HGPIN to prostate cancer through pharmacological means. Targeting precursor lesions (HGPIN) that may display simpler genomic aberrations relative to early stages of cancer in these high-risk groups may offer more promise to develop and test targeted interventions based on the biological differences reported in prostate carcinogenesis among African American men. Based on this evidence, African American men with biopsy-proven HGPIN are a subset of men who can be considered to be at high risk for prostate cancer and, thus, may be ideal candidates for chemoprevention interventions.

Although PSA and its kinetics are used to monitor disease progression, controversy exists regarding the
efficacy of PSA level as a screening tool due to its low rate of specificity; in addition, PSA levels are increased in benign prostatic diseases, such as benign prostatic hyperplasia (PSA concentrations can be ≤ 50% higher in some cases). African American men continue to have higher PSA levels and Gleason scores than white men, despite a narrowing of the differences in pathological stage. One study reported that African American men with prostate cancer and a Gleason score of 6 produce less PSA than white men. African American and white men had equal serum PSA and PSA masses despite significantly larger prostates in African American men and all other parameters being the same. Another report showed that men with higher levels of testosterone had higher levels of PSA even after taking into account other hormones, age, and race/ethnicity. While transcription of the PSA gene is transactivated by the androgen receptor (AR) with bound androgen, it is unclear whether circulating androgens influence circulating PSA levels. Men treated for prostate cancer with androgen-deprivation therapy experience a decline in serum PSA concentration, but this decline may be due to fewer cancer cells remaining to produce PSA and reduced testosterone available to all PSA-producing cells. Despite these drawbacks related to specificity, serum PSA as a continuous variable — as well as its doubling time and velocity — has been used in prostate cancer chemoprevention trials and in clinical practice to define risk categories.

Other biological differences in benign tissue and prostate tumors have been elucidated in African American and white men alike. Prostate tumors derived from African American men overexpress signaling receptors that may mediate increased proliferation, including EGFR and AR. On average, AR has a shorter polyglutamine repeat in African American men and, thus, increased AR activity. Reports have indicated decreased apoptosis and increased immunostaining for antiapoptotic protein B-cell lymphoma 2 (BCL2), suggesting that increased expression of BCL2 may decrease apoptosis and increase rates of tumor proliferation in African American men. Metastatic capacity may be higher in prostate tumor cells in African Americans because of the overexpression of several metastasis-related genes (AMFR, CXCR4, CCR7, and MMP9) as well as KI67 and CAV1 in African American men. Prostate tumors obtained from African American men may have decreased rates of tumor suppression.

Decreased TCEAL7 expression has been observed in tumors from African American men compared with tumors from white men. Reams et al observed that TCEAL7 expression in prostate cancer and in nonmalignant tissue was higher in white men compared with African American men. Chien et al demonstrated that TCEAL7 also inhibits the growth of ovarian cancer cells, suggesting that TCEAL7 is a tumor-suppressor gene and that varying expression levels of TCEAL7 between white and African American men may explain some of the disparities in the growth patterns observed in prostate cancer–derived tumors cells in these populations. Population studies comparing Japanese and African Americans have observed that short CAG repeats are more frequently associated with higher transactivational function in African Americans, possibly explaining racial differences in the incidence rate of prostate cancer between the 2 populations.

Taken together, these data suggest that there may be functional biological differences in the prostate tumors of African American men that may predispose them to a biologically more aggressive malignancy. However, these observations have not been validated in clinical trials targeting African American men.

Current Approach
Chemoprevention refers to the inhibition of preinvasive and invasive cancer and its progression or treatments of identifiable precancers. Chemoprevention efforts require an understanding of the mechanism of carcinogenesis, including signaling, metabolic, and genetic progression pathways. New technologies in genomics and proteomics have spurred this field of research. Use of this knowledge to develop pharmacological agents, botanicals, and biologics to reverse or halt the process of carcinogenesis is called chemoprevention.

Agents for chemoprevention include antiproliferation and antiprogression agents that prevent the growth and survival of cells already committed to become malignant. Finasteride and dutasteride, which block the conversion of testosterone to dihydrotestosterone, have been evaluated for chemoprevention of prostate cancer in large phase 3 chemoprevention trials. Although these agents significantly reduced the risk of prostate cancer, their use was also associated with an increased rate of high-grade disease, severely limiting their clinical adoption and underscoring the need to identify novel chemoprevention agents for prostate cancer.

Botanicals influence multiple biochemical and molecular cascades that inhibit mutagenesis, proliferation, induce apoptosis, and suppress the formation and growth of human cancers, thus modulating several hallmarks of carcinogenesis. In addition, these agents appear promising in their potential to impact the field of cancer chemoprevention, because they have a significantly superior safety profile than most available agents. Several botanicals have been characterized and used for hundreds of years, although existing challenges and limitations have hampered progress in this field. Multiple botanicals have been identified and appear promising for the chemoprevention of prostate cancer.
cancer. However, the slow pace of growth might be attributed to the regulatory protection of classical formulations and lack of standardization, quality control, a molecular mechanism-based approach in evaluation, a population-based normal range of biomarkers, laboratory practices, and few translational scientists engaged in conducting well-designed trials. However, several valuable lessons have been learned from previous chemoprevention trials. Critical requirements for moving botanicals from bench to bedside include adopting a systematic, molecular-mechanism based approach and utilizing the same ethical and rigorous methods such as those used to evaluate other pharmacological agents.

Chemoprevention trials using combinations of botanicals have demonstrated that synergy between agents can lead to lower doses, improved rates of efficacy, and fewer or less-severe toxicities. An assessment of the end points of chemoprevention trials whose results have been used to support approval of an agent for prostate cancer revealed that nearly all have been approved on the basis of intraepithelial neoplasia. Intermediate biomarker end points must be identified, validated, and obtained using noninvasive techniques without compromising the safety to men in chemoprevention trials. To reduce patient burden, these markers must be obtained from accessible organs and during the normal course of clinical surveillance. Randomized placebo control trials and the long-term follow-up and monitoring of patients and study participants are critical to meet the requirements of the US Food and Drug Association and to promote the acceptance of new agents into the marketplace.

**Green Tea Catechins**

The Table summarizes the clinical, molecular, and biological characteristics relevant to prostate cancer in African American men and compares them with the effects of green tea catechins used to modulate those characteristics.

Laboratory studies have identified epigallocatechin gallate (EGCG) as a potent chemopreventive agent because it affects various key molecular processes in prostate carcinogenesis that help induce apoptosis and inhibit tumor growth and angiogenesis. Preclinical studies have demonstrated chemopreventive efficacy in prostate cancer, showing that it has significant activity on prostate cancer cells. Phase 1/2 studies have demonstrated the bioavailability and tolerance of green tea catechin at various ranges of doses of EGCG.

Although several mechanisms exist by which EGCG may operate in prostate carcinogenesis, EGCG selectively inhibits the proteasome activity in intact human prostate cancer cells and accumulates in IκBα and p27 proteins, thus leading to growth arrest. High-grade green tea polyphenol extract, which is a mixture of tea catechins with more than 50% of EGCG, inhibits the proteasomal chymotrypsin-like activity with a half maximal inhibitory concentration value of 7 μM. The half maximal inhibitory concentration value for trypsin-like activity is higher than 100 μM.

### Table. — Summary of Relevant Characteristics of Prostate Cancer and the Effects of Green Tea Catechins in African Americans

<table>
<thead>
<tr>
<th>Characteristic of Prostate Cancer</th>
<th>Effect of Green Tea Catechins</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
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<tr>
<td>Increased frequency of HGPIN</td>
<td>Men with HGPIN had significantly reduced disease progression</td>
</tr>
<tr>
<td>Higher PSA levels</td>
<td>Men with HGPIN had lower PSA levels than the control arm</td>
</tr>
<tr>
<td>Higher Gleason scores at diagnosis</td>
<td>Men given short-term daily doses had significant decreases in serum PSA levels</td>
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<tr>
<td><strong>Molecular</strong></td>
<td></td>
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<tr>
<td>Increased Proliferation</td>
<td>Decreased Proliferation</td>
</tr>
<tr>
<td>EGFR overexpression</td>
<td>In vitro models</td>
</tr>
<tr>
<td>AR overexpression</td>
<td>In vivo models</td>
</tr>
<tr>
<td>Increased androgen-receptor activity</td>
<td>Reduced androgen-receptor signaling and activity</td>
</tr>
<tr>
<td><strong>Decreased Apoptosis</strong></td>
<td>Induced Apoptosis Induction</td>
</tr>
<tr>
<td>Increased expression of BCL2</td>
<td>Various mechanisms (eg, reduced BCL2 expression)</td>
</tr>
<tr>
<td>Increased Metastatic Capacity</td>
<td>Inhibition of Invasion and Metastasis</td>
</tr>
<tr>
<td>Overexpression of AMFR, CXCR4, CCR7, MMP9, Ki67, and CAV1</td>
<td>Various mechanisms (eg, MMP9, MMP2 suppression)</td>
</tr>
<tr>
<td>Decreased Tumor Suppression</td>
<td>Reactivation of Silenced Tumor-Suppressor Genes</td>
</tr>
<tr>
<td>Downregulation of TCEAL7</td>
<td>Restores balanced proliferation</td>
</tr>
</tbody>
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HGPIN = high-grade prostatic intraepithelial neoplasia, PSA = prostate-specific antigen.
demonstrating that high-grade green tea polyphenol extract preferentially inhibits the proteosomal chymotrypsin-like activities over other activities.93

Kim et al.126 investigated the safety and efficacy of high-grade green tea polyphenol extract in an animal model. Their goal was to reduce the progression of prostate adenocarcinoma in transgenic mice. Mice treated with the green tea extract had significantly fewer tumors and decreased tumoral sizes compared with the animals that did not receive the extract. The high-grade green tea polyphenol extract also significantly inhibited metastasis in the treated mice in a dose-dependent manner. Therefore, the data suggest that high-grade green tea polyphenol extract is an effective chemopreventive agent in preventing the progression of prostate cancer to metastasis in a mouse model.126 These findings provide evidence for the safety and chemopreventive effect of this green tea polyphenol extract for preventing metastatic spread in prostate cancer.

Based on the results of previous studies, a placebo-controlled, randomized clinical trial was conducted of the high-grade green tea extract in 97 men with HGPIN, atypical small acinar proliferation, or both conditions.64,92,119-121 No differences were observed in the number of prostate cancer cases. The cumulative rate of prostate cancer plus atypical small acinar proliferation among men with HGPIN but without atypical small acinar proliferation at the start of the study was researched. The data revealed a statistically significant decrease in this composite end point: 3 of 26 (high-grade green tea polyphenol extract group) vs 10 of 25 (placebo group).126 A decrease in diagnoses of atypical small acinar proliferation was also seen among those receiving the green tea extract, as was a decrease in serum PSA level, compared with those assigned to placebo.126

Intake of a standardized, decaffeinated green tea catechin mixture every day for 1 year accumulated in plasma and was well tolerated, and researchers saw that its consumption significantly reduced the cumulative rates of prostate cancer and atypical small acinar proliferation among men with HGPIN who did not have atypical small acinar proliferation at baseline.137 Three of the 9 African American men in the study progressed to atypical small acinar proliferation or prostate cancer after 1 year, but no such progression was seen among those assigned to the high-grade green tea polyphenol extract arm.137 This disease progression rate from HGPIN in the placebo arm was higher than US norms and in white men assigned to the placebo arm of this trial (20%).92,64,65,137,138 In men with a baseline diagnosis of atypical small acinar proliferation, the diagnostic rates of cancer at 1 year were similar, regardless of treatment arm assignment or race.137 Overall, a significant increase in plasma EGCG concentration was observed, as was a reduction of serum PSA and disease progression from HGPIN to atypical small acinar proliferation or prostate cancer with green tea catechin treatment. Although these are early observations with small sample sizes, these data are provocative and warrant further evaluation in a well-powered clinical trial targeting African American men with HGPIN, because they suggest that green tea catechins have the potential to decrease the risk of progression to atypical small acinar proliferation and, subsequently, prostate cancer.137 However, the study was limited by its small sample size of African American men, so the researchers were unable to make comparisons among white men with HGPIN in other blood and tissue-based biomarkers.

Experimental models to address the fundamental molecular pathways of green tea catechin have yet to be validated in green tea catechin–treated tissue samples from clinical trials.118 In addition to developing and refining the fundamental pathways of green tea catechin, future studies evaluating these molecular pathways should define intermediate biomarkers of prostate carcinogenesis. However, obtaining sufficient tissue from prostate biopsies from precursor lesions in prevention trials continues to present a challenge. Therefore, it will be important to prioritize intermediate biomarkers available for evaluation based on the robustness of evidence and relevance to the agent, the potential molecular mechanism, and the patient cohort and stage of disease targeted in future studies.92,95

Green tea catechins target every major clinical prostate cancer characteristic reported in African American men (see Table).11,51,52,58,59,68-75,98-116 They may do this by acting through the biological mechanisms especially relevant to African American men, including reducing proliferation, inducing apoptosis, and decreasing tumoral metastatic capacity. Thus, it is our opinion that green tea catechins are a promising candidate for the chemoprevention of prostate cancer in African American men.

Conclusions

Prostate cancer in African American men is a major public health problem with significant morbidity and mortality rates. A variety of laboratory approaches are being applied to unravel the molecular pathogenesis of prostate cancer. African American men with a family history of prostate cancer, diagnosed with high-grade prostatic intraepithelial neoplasia prior to age 50 years, represent an ideal target population for chemoprevention. Green tea catechins have been characterized and evaluated as agents able to target multiple pathways that address the underlying biology of prostate carcinogenesis in African American men. Assessing the efficacy of this intervention might eventually translate into clinical use in high-risk populations. It is our opinion that the greatest challenge to evaluating prom-
is agents for chemoprevention is the recruitment and retention of African American men in randomized clinical trials, which will require multiple approaches, actions, and activities for achieving meaningful advances. The process is a complex and progressive one, including the formation of trusting partnerships with target populations and their circles of influence, power sharing, priority setting, capacity building, education and training, the transparent sharing of data and information, the development of goals, and insisting on community involvement in the research.

References


