Review

5-α-Reductase Inhibition and Prostate Cancer Prevention

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Abstract

Studies of prostate biology support the concept that dihydrotestosterone is the principal androgen responsible for normal and hyperplastic growth of the prostate gland. Cancer is a process of malignant transformation evolving over time, involving cellular growth and division. Therefore, an altered endocrine state, such as suppression of dihydrotestosterone activity, may have an impact on prostate cells inhibiting carcinogenic transformation. In vitro and in vivo preclinical observations support this hypothesis. A placebo-controlled randomized trial using finasteride, an inhibitor of the enzyme that converts testosterone to dihydrotestosterone, is planned. The endpoint of this trial will be reduction of prostate cancer incidence.

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer and the second most common cause of cancer death in American men. Last year nearly 165,000 American men were diagnosed with prostate cancer and approximately 35,000 died of it (1). More than half the cancers are beyond the prostatic capsule at the time of diagnosis. Therapy for advanced disease is not curative. Early detection, currently under investigation, has not yet been proven to impact on mortality (2-5). The National Cancer Institute has launched a large randomized trial to determine the impact of screening with digital rectal examination and serum PSA on prostate cancer mortality (6). Another line of investigation to pursue is primary prevention. Recent leads in the understanding of the biology of the prostate gland and the development of drugs that block the formation of androgenic growth factors raise the possibility of new prevention strategies.

Clues to the prevention of a malignancy may be found through study of its etiology, epidemiology, and biology. There is accumulating evidence that androgens have a permissive role in, and indeed may promote, prostate carcinogenesis. It has been suggested that prostate cancer is extremely rare in men castrated before puberty (7-9). It also has been reported that populations with lower serum androgen levels have a lower incidence of prostate cancer (10). Androgen ablation leads to regression of clinical prostate cancer. These facts suggest that prostate cancer can be prevented if tolerable androgenic reduction, inhibition, or blockade can be applied. We will discuss the rationale for a prostate cancer primary chemoprevention study using finasteride, an enzyme inhibitor that blocks the conversion of T to DHT.

Epidemiology of Prostate Cancer

Incidental histological prostate cancer is prevalent in men as young as 30-40 years old (11). However, the risk for clinically significant prostate cancer does not begin to increase sharply until about age 60. Although heredity and environmental factors have been implicated in the etiology of clinical prostate cancer, the vast majority of victims have no known risk factors other than male gender and age (12-14). However, there are significant racial differences in the incidence of clinically diagnosed prostate cancer. The age-adjusted incidence of clinically diagnosed prostate cancer is 142/100,000 for African-American men and 108.5/100,000 for white American men (15). African and Japanese men have a markedly decreased risk of developing clinically significant prostate cancer when compared with Americans (16).

Autopsy studies have shown that more than 30% of men over the age of 50 have an incidental finding of prostate cancer at death. Although substantial racial and cultural variance in the number of clinically significant prostate cancers exists, there is far less racial or cultural variation in the number of incidental prostate cancers at autopsy (17-19). This suggests a common rate of initiation in such diverse populations, but different rates of promotion or tumor progression. Migratory population patterns implicate environmental influences, such as diet, as causal cofactors of aggressive prostate cancer (20). It has been suggested that high dietary fat intake may cause increased production of androgens, which may lead to an increased incidence of clinically significant prostate cancer (21-23).

The precise role of androgens in the etiology of human prostate cancer is unclear. There are data implying that the amount of androgen available over time may be related to prostate cancer risk. It has been asserted that prostate cancer is rare in men castrated before puberty or early in adulthood (7-9). Ross et al. (10) observed that young adult African-American men have higher circulating T concentrations when compared with a similar group of young adult white men. It has been suggested that this may explain the underlying differences in the incidence of clinically significant prostate cancer between the two races (7). Additional support for the role of androgens in prostate cancer is the observation that 5-α-reductase activity is decreased in low risk populations such as Chinese (24) and Japanese (16) men...
compared with American men. The enzyme 5α-reductase is the enzyme that converts T to the more potent androgen DHT (25).

Hormonal Dependence of the Prostate
The prostate is an androgen dependent organ. Androgens promote cell proliferation and inhibit prostate cell death (26). The enzyme 5α-reductase is a nuclear membrane-bound NADPH-dependent 3β-substituted 5α-oxido-reductase. Its primary function is to convert T to DHT (27). There are two known 5α-reductase isoenzymes. 5α-reductase-1 is present in low levels in a number of tissues and 5α-reductase-2 is found in androgen-sensitive cells of the skin and prostate (28, 29). The testes and adrenal glands secrete T into the bloodstream. Then a substantial fraction of T diffusing into 5α-reductase-containing cells is converted irreversibly to DHT. Although both T and DHT can bind to the cellular prostate androgen receptor and produce androgen mediated effects, DHT is more potent than T. When compared with T, DHT exhibits a higher binding affinity for and lower dissociation rate from the androgen receptor, and the DHT receptor complex has greater stability and a higher binding affinity for DNA (30). DHT promotes development of prostate cells, BPH, and possibly serves as a promoter for prostate cancer.

An observation of nature documents the key role that 5α-reductase-2 and DHT play a role in prostate development. Males with inherited homozygous 5α-reductase deficiency are pseudodermaphrodites with a female or ambiguous external genitalia until puberty. The normal increase in T production at puberty induces development of a small phallus and virilization. After puberty, individuals with the enzyme deficiency often become morphologically and functionally normal males, although they do not develop acne or male pattern baldness. They have an underdeveloped prostate even though they maintain normal serum T levels after puberty. No other illnesses are associated with 5α-reductase deficiency, and females with the inherited enzyme deficiency have no known medical sequelae (31–33).

Androgens are significant in the biology of BPH. Men with testicular hormonal dysfunction rarely develop BPH and orchiectomy has long been used to treat severe BPH (34). Therapy with the 5α-reductase inhibitor, finasteride, causes decreased serum prostatic DHT levels, regression of BPH, and a reduction in serum PSA (35, 36). Thus, DHT is the significant hormone in prostatic hyperplasia and prostate biology.

Role of Androgens in Human Prostate Cancer
The hormonal sensitivity of prostate cancer has been exploited clinically since 1941, when the Nobel Prize-winning work of Huggins and Hodges established the suppressive effects of castration on prostate cancer (37). Hormonal treatments that remove androgens or block their cellular effects are used commonly in prostate cancer therapy. Widely used agents include: estrogens (e.g., diethylstilbestrol), synthetic luteinizing hormone agonists which inhibit gonadotrophin secretion (38), and flutamide, an antiandrogen that competitively inhibits androgen binding to the cellular androgen receptor (39). Most hormonal therapies are similar in efficacy. However, tumor progression usually occurs within 2 years, and the disease is uniformly refractory to further hormonal manipulation.

It is not possible to predict which tumors will respond to hormonal therapy. Androgen receptor assays are not widely available and have not provided information useful in guiding clinical care (40). In general, more differentiated cells are thought to be more sensitive to hormonal manipulation. Well differentiated prostate tumors generally have higher numbers of androgen receptors when compared with less differentiated prostate malignancies (41, 42). Cells in the carcinogenic process progress at variable rates from differentiated to less differentiated (43). Over time, they become a biologically heterogeneous group of cells consisting of androgen-dependent, -responsive, and -independent cells (44).

Laboratory Models of Prostate Cancer
All major rodent models involve administration of pulse doses of a chemical carcinogen followed by chronic administration of high doses of androgens (45). This means that available rodent carcinogenesis models are not well suited for testing the hypothesis that lowering androgenic stimulation with 5α-reductase inhibition will prevent cancer. However, the very fact that androgens are necessary to promote prostate cancer development in laboratory animals is in itself supportive of the theory that decreasing androgenic stimulation can lower prostate cancer risk.

Several studies using prostate tumor in tissue culture or rodent implant models have demonstrated that 5α-reductase inhibitors can inhibit the progression of some prostate cancers (46, 47). PC3 and DU145 are moderately androgen-sensitive human prostate cancer cell lines. In tissue culture, finasteride causes dose-dependent growth inhibition of these cell lines (48). The human prostate cancer PC-82 is a moderately differentiated human prostatic adenocarcinoma. 5α-reductase inhibitors cause a reproducible inhibition of tumor growth when the tumor is implanted in treated mice. Growth inhibition of hormone-sensitive Dunning R-3327G rat prostate tumor implants by 5α-reductase inhibition also has been demonstrated in rodents (49–51).

The Dunning R-3327G prostate cancer cell line has 5α-reductase levels similar to those found in normal human prostate tissues and human prostate cancers (48–50). Growth of the androgen-responsive Dunning R-3327H subline is not affected by administration of 5α-reductase inhibitors, nor is DHT tissue content measurably reduced. Although the tumor is androgen dependent, as demonstrated by response to orchiectomy, it has tissue 5α-reductase activity at least six times that of the Dunning R-3327G (48–50).

It is possible that inhibition of 5α-reductase would exert progressively less influence as a tumor increases in size and cells progress to a less differentiated state. Therefore, hormonal manipulations, such as DHT inhibition, may exert the greatest influence at the earliest stages of tumor development and progression. Comparison of the DHT/DNA ratios in intraprostatic human prostate cancer tissues demonstrates that more differentiated malignant tissues have higher ratios (52, 53).

Nonetheless, the treatment of men with stage D prostate cancer with 5α-reductase inhibitors does cause moderate decreases in serum PSA. Although the clinical significance of this decline is unknown, it demonstrates that DHT and DHT inhibition may exert some influence, even on undifferentiated metastatic prostate cancer (54).
5-α-Reductase Inhibition

Although 5-α-reductase inhibitors have some antitumor activity, anticancer activity is not necessary for a drug to prevent cancer. Decreasing the androgenic stimulation of prostate cells may lower the probability that they will enter the carcinogenic process. Until now it has been difficult to test this hypothesis. Most available hormonal manipulations to prevent prostate cancer are impractical because of their toxicities. Drugs that mimic castration by inhibition of androgen synthesis or by blocking T action routinely cause impotence, gynecomastia, breast tenderness, loss of libido, and other symptoms. But most androgenic effects in tissues other than the prostate are mediated by T rather than DHT. As stated earlier, adults with inherited 5-α-reductase deficiency have no ill effects as a result of decreased DHT levels.

A number of 5-α-reductase inhibitors have been synthesized and pharmacological intervention is becoming possible. Finasteride was the first 5-α-reductase inhibitor to enter clinical trial. Therefore, there is substantial information on the toxicity profile of finasteride. It has been studied extensively for the management of BPH and has been approved by the United States Food and Drug Administration for that indication.

Preclinical Toxicology

Finasteride is a steroidal analog of T. It functions as a reversible competitive inhibitor of 5-α-reductase. In preclinical studies, the oral lethal dose in 50% for mice, rats, and dogs was from 300 to 1000 mg/kg, in all cases greater than 3000 times the effective human dose. Therapeutic concentrations of finasteride have not demonstrated mutagenicity in genetic toxicity assays assessing for evidence of drug-induced DNA damage or chromosomal aberration. Studies in animals show no evidence of carcinogenicity. Drug-related benign Leydig cell adenomas have been observed in male mice treated chronically with 250/kg/day, but not at lower doses (55). Finasteride has been tested in animals for effects on the fertility and for teratogenicity. Finasteride has no significant effects on fertility of male rabbits. The drug does not influence rabbit mating behavior, spermatogenesis, or the fertilizing effects of sperm. In male rats, a rapidly reversible decrease in fertility is seen. This effect is caused by a species-specific effect on seminal plug formation, which is essential for rat fertility, but not relevant to humans. Rat studies demonstrate that in utero exposure to the drug can cause developmental abnormalities in male offspring. These male offspring have male organs internally but an external female appearance. This is an expected pharmacological effect of the drug, again irrelevant to use in human males.

Phase I Clinical Studies and Human Toxicology

Male subjects treated with finasteride have systemic T and DHT levels very similar to those of male pseudohermaphrodites with inherited 5-α-reductase deficiency (56). Finasteride causes a 75% decrease in serum DHT levels, an 80% percent decrease in intraprostatic DHT, and a 10% increase in serum T. Despite the 10% increase in serum T, all values were within the clinically normal range in several large trials. Although very high concentrations of T can interact with androgen receptors similar to DHT, the increased T levels found in male pseudohermaphrodites are not high enough to promote prostate growth (25).

Finasteride is absorbed readily from the gastrointestinal tract when taken orally. The serum half-life of orally administered finasteride is approximately 8 hours. The drug is metabolized by the liver and kidney with 57% in feces and 39% excreted in the urine. Humans easily can tolerate a single dose of 400 mg, although single doses as low as 0.2 mg lead to marked suppression of serum DHT levels persisting for up to 4 days. Hormonal changes because of finasteride therapy are entirely reversible. DHT levels return to pretreatment values within 14 days of stopping treatment (57). In two double-blind, placebo-controlled clinical trials, over 1600 patients with BPH were randomized to three treatment groups: placebo; 1 mg of finasteride per day; or 5 mg of finasteride per day, and followed for compliance for at least 12 months (58). Both doses suppress serum DHT levels to anorched levels, although the 5 mg dose produces slightly lower levels than the 1 mg dose. Study participants were followed with magnetic resonance imaging or transrectal ultrasound and all had urinary flow studies. After 1 year of therapy, finasteride-treated patients at both dose levels had a mean 20% reduction in prostate volume and approximately one-third had a 3 ml/s increase in urinary flow rate. These studies also demonstrated a statistically significant decrease in urinary symptoms compared with the control group. Patients taking finasteride experience a 40–50% reduction in serum PSA. An open extension study, using 5 mg/day, has continued and some patients have been treated for more than 3 years. The drug continues to suppress DHT levels and retard prostate growth for as long as it is administered. More than 40% of men have a sustained increase in urinary flow of 3 ml/s or greater at the end of 2 years of therapy (58).

In the randomized, placebo-controlled trials, there was no difference in the safety profile between the 1-mg and 5-mg doses. Finasteride has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational activity (59). Plasma-luteinizing hormone, follicle-stimulating hormone, cortisol, and estradiol levels are not affected significantly by finasteride. No drug effect has been observed on serum lipid profiles, glucose tolerance, or any routine chemistry or hematologic evaluations (55).

Both finasteride treatment groups were similar to the placebo group in the incidence and types of side effects observed. The statistically significant findings, when compared with placebo, were a slightly increased number of sexually related side effects in the finasteride-treated arms. These side effects were: decreased libido in 5.4% (finasteride-treated arms) versus 1.3% (placebo arm); impotence in 4.1% (finasteride) versus 1.7% (placebo); and decreased ejaculate volume in 4.4% (finasteride) versus 1.7% (placebo) (58). The frequency of these drug effects was stable with prolonged use. All were reversible when therapy was discontinued, and indeed, a recent study indicates that sexually related adverse experiences decrease even if finasteride therapy is continued (55, 60). One-third of men having adverse symptoms reported that the symptoms ceased despite continuation of the drug. Patients with sexually related complaints did not have different hormonal profiles when compared with others on finasteride (55).

As expected, finasteride does decrease ejaculate volume. This is not subjectively noticed. A mean 25% decrease in ejaculate volume was observed in a double-blind, placebo-controlled study of normal volunteers. No significant differences between treatment groups were observed in total sperm/ejaculate, sperm motility, or morphology (55).
Testing the Hypothesis
A chemopreventive agent must have very few side effects, and benefits beyond prevention of prostate cancer are desirable. Given its excellent safety profile and the possibility that it may prevent BPH, finasteride may be very suitable for long-term administration as a cancer chemopreventive agent. A randomized, double-blind, placebo-controlled trial is necessary to determine definitively if DHT inhibition will reduce the incidence of prostate cancer. The National Cancer Institute and the multispecialty cooperative cancer treatment groups are beginning such a trial.

The trial will enroll 18,000 men, 55 years of age and older. Each participant must be in generally good health, with no evidence of prostate cancer by digital rectal exam and serum PSA of 3 ng/ml or less (Hybritech assay). Participants can have some symptoms of BPH but they cannot be so significant that the patient or physician believes a transurethral resection of the prostate will be needed within a year of entry. Entrants will be randomized to finasteride (5 mg/day, orally) or an inactive placebo.

The primary objective of the trial is to demonstrate a decreased incidence of prostate cancer after 7 years of finasteride therapy, when compared with the placebo group. Each participant will be treated for 7 years, and followed for life. Although the trial is designed to assess decreased prostate cancer incidence, there are plans to gather data on all trial participants.

During the trial, participants will be followed for development of prostate cancer with an annual digital rectal examination and measurement of serum PSA. To assure standardization, serum will be shipped to a central laboratory for PSA determinations. The laboratory also will measure serum DHT levels of subjects to assess for compliance and to determine if there is contamination of the placebo arm. Participants and their physicians will be blinded to the exact serum PSA values because the effect of finasteride potentially may unblind participants. Values will be reported to the subjects and their physicians as normal or abnormal.

To assure an equal opportunity for PSA-driven detection of prostate cancer in both arms, men who receive placebo with a serum PSA over 4.0 or a significant increase in serum PSA will be evaluated for prostate cancer with a sextant biopsy of the prostate, and the same proportion of compliant men who receive finasteride (those with the highest PSAs) also will receive a prostate biopsy. It has been suggested that 5-a-reductase therapy may decrease PSA secretion from benign prostatic tissue more so than from malignant tissue (61). If this is true, finasteride may increase the sensitivity and specificity of serum PSA screening. In an effort to reduce biases in prostate cancer detection for or against the finasteride arm, all men in the trial will receive a sextant prostate biopsy at the end of 7 years on study. It is realized that some study subjects may need prostatectomy because of BPH. All prostate cancers diagnosed during the trial will be noted as an incidence endpoint and the patients will continue to be followed off treatment. All biopsies, and when possible, whole prostate specimens, will be reviewed centrally by a panel of expert pathologists. Findings will be reported with as much information as possible to include tumor sizes and grades. The trial design allows for a 90% power to detect a 25% difference in prostate cancer incidence between the two groups.

Such a trial can have a number of advantages beyond determining if prostate cancer can be prevented. The study is a unique opportunity to assess finasteride in the prevention of BPH. Significant human and financial burdens can be relieved if the trial finds that several years of 5-a-reductase inhibition before the onset of significant symptoms of prostatic hyperplasia decreases the need for transurethral resection of the prostate. Prospectively following a large group of aging men can provide valuable data on the natural history and risk of prostatic diseases and quality of life in the aging male. There is a need for clarification of the natural history of a number of prostate pathologies. Prostatic intraepithelial neoplasia and adenomatous atypical hyperplasia are poorly understood entities. At this time, one can only speculate on the incidence or significance of diagnosed prostatic intraepithelial neoplasia or adenomatous atypical hyperplasia (62). This trial may provide data such that individual risk for prostate cancer can be quantified and future trials can be designed to enroll men at high risk. Serum and tissues will be stored in a repository allowing for intermediate markers of neoplasia to be developed and evaluated at a later date. The value of early detection and the currently available screening technologies are the subject of several ongoing and planned clinical trials. This chemoprevention trial, with a rigorous screening program, also will yield data addressing the characteristics of prostate cancer screening methods in men receiving finasteride and placebo. The trial will generate data on the effect of prolonged 5-a-reductase treatment on serum PSA concentration and help assess the concept of serial changes in serum PSA over time as a screening tool.

Summary
The concept that androgens promote prostate cancer is widely accepted. Laboratory animal models develop prostate cancer at increased rates when treated with high doses of androgen. Male pseudohermaphrodites with inherited homozygous 5-a-reductase deficiency and a vestige of prostate tissue are proof of the importance of DHT to prostate growth and development. The effectiveness of finasteride in the treatment of BPH is further evidence of the importance of DHT in prostate growth. There are data implying that humans with low 5-a-reductase activity have lower incidence of prostate cancer (10). If DHT is a promoter of carcinogenesis, pharmacologically decreasing the DHT stimulus on prostate tissue may serve as an antipromoter of prostate cancer development and growth at very early stages of the carcinogenic process. The availability of the well tolerated 5-a-reductase inhibitor, finasteride, makes prostate cancer chemoprevention a possibility. It is estimated that more than 500,000 men world-wide currently are being treated for BPH with finasteride.

A randomized chemoprevention trial will begin in the near future. Although the primary objective of the finasteride chemoprevention trial will be to assess the ability of the drug to prevent the development of prostate cancer and its progression, the study will also be a vehicle through which we can gain a better understanding of a number of questions about prostate biology and epidemiology. This study will facilitate ancillary studies investigating intermediate markers, surrogate endpoints, predictors of tumor behavior, and an understanding of benign and malignant tumor pathology.

References


5-Alpha-reductase inhibition and prostate cancer prevention.

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