# Drug Therapies for Eradicating High-Grade Prostatic Intraepithelial Neoplasia in the Prevention of Prostate Cancer

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*High-grade prostatic intraepithelial neoplasia (HGPIN) is a precursor to invasive prostate cancer observed as an isolated entity in a growing subset of men undergoing prostate biopsy. The presence of HGPIN predicts an increased risk of 1) coexisting occult prostate cancer at baseline and 2) delayed progression to prostate cancer. As such, men with HGPIN represent a population at high risk for the development of prostate cancer. Because the current recommended therapy is observation and delayed-interval biopsies until cancer develops, a well-tolerated therapeutic agent capable of interrupting the progression of HGPIN to cancer is highly desirable. Given the known cancer-stimulatory effects of estrogens in the prostate, the use of selective estrogen receptor modulators (SERMs) to provide an antiestrogen effect represents a novel strategy for prostate cancer prevention. Recent phase II data from trials using toremifene in the treatment of men with HGPIN validate the use of SERMs as a rational and provocative strategy for the prevention of prostate cancer.*
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Prostate cancer prevention is the most likely strategy to reduce prostate cancer death. Furthermore, accurate risk stratification allows selection of individuals who are appropriate candidates for prevention strategies. In the specific case of prostate cancer, prevention, as a therapeutic approach, is particularly appealing because of 1) the significant concern regarding overtreatment of early cancers, 2) the difficulty in defining metastatic potential at an early point in the disease's natural history, and 3) the variability in disease phenotype at later stages.

Several potential high-risk cohorts have been defined for prostate cancer detection. Men with a family history of prostate cancer in a first-degree relative and those of African American descent have been shown to have a 2- to 2.5-fold relative risk of disease.[1] Clearly, these are individuals for whom a defined long-term risk of prostate cancer exists. Among men with elevated serum prostate-specific antigen (PSA) levels, the relative risk of cancer is increased at the time of presentation, but following negative biopsy, the long-term risk of prostate cancer is poorly defined. As a number of factors may increase the serum PSA level, it is not clear whether individuals with an elevated PSA level and a negative biopsy are truly representative of a high-risk cohort.

Histologic evaluation of the prostate at the time of negative biopsy may allow further selection of true high-risk cohorts among men with elevated or normal serum PSA. At highest risk are men with demonstration of atypia or atypical small acinar proliferation. In these cases, small clusters of glands suspicious for cancer foci are identified by the pathologist.[2-4] As such, the pathologist suspects cancer but is not comfortable making the diagnosis. In these individuals, a high likelihood of occult malignancy exists.[4-7] If prevention efforts are targeted to this group, they are essentially intended to prevent the progression of existing cancer.

A distinction must be made between atypia and high-grade prostatic intraepithelial neoplasia (HGPIN), which is believed to represent a premalignant lesion.[8-10] Individuals with HGPIN are known to have a high risk of occult malignancy as well as a risk of progression to prostate cancer at a delayed interval. As such, individuals with isolated HGPIN may represent the best example of men in whom the progression to prostate cancer has begun and appear to be ideal candidates for prevention strategies.

## Does HGPIN Truly Define a High-Risk Cohort?

The clinical significance of HGPIN has been widely debated. Although noted in association with the majority of surgically resected prostate cancers, its true premalignant potential has been difficult to define.

HGPIN is histologically characterized by increased proliferation and anaplasia in cells lining the prostate ducts. Individual cells carry morphologic features, such as prominent nucleoli, which are characteristic of prostate cancer.[8,11,12] Although the cells are morphologically bizarre, the glands are normal ducts by virtue of the presence of a basal cell layer. Histologically, HGPIN and prostate cancer have been observed in the same duct, providing strong correlative evidence of a spectrum of disease.

In autopsy studies, HGPIN does appear to precede prostate cancer in some cases.[13-16] Within each subsequent decade of life, the prevalence of HGPIN serially increases. In addition to an increasing risk with age, HGPIN is demonstrated at slightly higher prevalence among African Americans, who are known to be at higher risk for prostate cancer (Table 1).[13,14,16] Multifocal HGPIN lesions were also more common in African American men. It is well recognized that the majority of autopsy cancers are of no clinical significance. In African American men who are known to have the highest mortality rate from the disease, the prevalence and extent of HGPIN was significantly greater in radical prostatectomy specimens obtained from this cohort, suggesting a link between HGPIN and clinically important cancer.[17] This parallel distribution of HGPIN and cancer, along with the temporal relationship and increasing prevalence of HGPIN in clinical prostate cancers for African American men, strongly implicates HGPIN as a precursor to invasive prostate cancer.

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Table 1
Prevalence of HGPIN and Prostate Cancer in African American (AA) and Caucasian (C) Autopsy Cases

| Age Group, y | HGPIN, % | | Prostate Cancer, % | |
|---|---|---|---|---|
| | AA | C | AA | C |
| 20-29 | 0 | 0 | 3 | 0 |
| 30-39 | 6 | 3 | 26 | 33 |
| 40-49 | 10 | 9 | 29 | 36 |
| 50-59 | 44 | 38 | 44 | 62 |
| 60-69 | 67 | 60 | 67 | 60 |

HGPIN, high-grade prostatic intraepithelial neoplasia.
Data from Sakr WA et al.[16]

## Current Management of HGPIN in Clinical Practice

In managing HGPIN, the clinician must contend with 2 basic concepts: 1) ruling out coexisting cancer, and 2) ruling out cancer progression over time. The observation of a high rate of HGPIN prevalence among radical prostatectomy specimens predicts a high likelihood of coexistent cancer when HGPIN is found on routine biopsy. Even in individuals with no cancer identified on repeat biopsy, the clinician should have a strong

Table 2
Comparison of Cancer Detection on Follow-Up Biopsy Among Men Diagnosed with HGPIN on Initial 12-Core Sampling*

| Biopsy | n | Cancer, n (%) | HGPIN, n (%) | Atypia, n (%) | Benign, n (%) |
|---|---|---|---|---|---|
| < 1 y[24] | 43 | 1 (2.3) | 20 (46.5) | 1 (2.3) | 20 (46.5) |
| 3 y[25] | 31 | 8 (25.8) | 11 (35.5) | 0 | 12 (38.7) |

*Although few cancers are diagnosed on biopsy within 1 year of follow-up, by 3 years, 25.8% of men are found to have cancer.
HGPIN, high-grade prostatic intraepithelial neoplasia.
Data from Lefkowitz GK et al.[24,25]

suspicion of undiagnosed foci of microscopic cancer.

In the first report of repeat biopsy for HGPIN, 21 men diagnosed with HGPIN on sextant sampling underwent repeat biopsy.[18] Cancer was identified in 57% of the men by transrectal ultrasound–directed biopsy. In follow-up studies, the rate of cancer detection has varied, but in studies that specifically evaluated men diagnosed with HGPIN on sextant biopsy, the rate of cancer detection on immediate repeat biopsy has generally ranged from 30% to 50%.[9,19-23]

With the advent of extended field biopsy, the ability to find HGPIN has increased, perhaps slightly increasing the incidence of HGPIN as a pathologic diagnosis. Additionally, because of better sampling in the initial biopsy, the yield of immediate repeat biopsy has declined. In a study of 43 men undergoing repeat biopsy within a year of being diagnosed with HGPIN on 12-core extended field sampling, we found only 1 man (2.3%) with prostate cancer (Table 2).[24] Additionally, only 46.5% of the men were found to have HGPIN on repeat biopsy, illustrating that when detected on extended field sampling, HGPIN is more likely to be smaller in volume.

Other investigators have shown similar results when evaluating repeat biopsy for HGPIN among men diagnosed on extended field biopsy. Recently, Moore and colleagues[7] evaluated 22 men with HGPIN diagnosed on extended peripheral zone biopsy. A total of 33 repeat biopsies were performed, with 11 men undergoing 2 serial repeat samplings. Only 1 cancer was identified among this cohort. Interestingly, 5 men were found to have atypical small acinar proliferation on repeat biopsy, further illustrating the concept that many men with HGPIN likely have small foci of cancer that are not detected at the time of aggressive routine sampling.

Based collectively on our data and that of others, we believe that a 12-core sampling of the peripheral zone is adequate to rule out coexisting cancer in the majority of patients with HGPIN. Individuals who might benefit from immediate repeat biopsy include those believed to be at high risk for cancer based on other clinical parameters. Men with PSA > 10 ng/mL, a strong family history, or a recent rapid rise in serum PSA should be considered for early repeat biopsy with sampling of the transition zone of the gland. In these men, the suspicion is not that of progression of HGPIN to cancer but rather that of an unsampled coexisting cancer. For men with none of these features, observation of serial PSA measurements with consideration of delayed-interval biopsy (DIBx) should be sufficient.

If we believe HGPIN is truly a precursor to invasive cancer, then men with HGPIN should be longitudinally monitored by biopsy, independent of serum PSA levels. As a follow-up to our study of immediate repeat biopsy, we undertook an evaluation of the delayed risk of prostate cancer in men with HGPIN. Thirty-one men with HGPIN diagnosed on a minimum of 12-core sampling were asked to undergo repeat sampling 3 years after the initial diagnosis.[25] A total of 8 men (25.8%) were found to have prostate cancer. This increase in cancer diagnosis at 3 years (Table 2), compared with 2.3% if repeating biopsy with 1 year, implies that men either undergo a progression from HGPIN to cancer or that small cancers progress to a size at which they are detectable. In either case, the yield of repeat biopsy in this study justifies the use of routine DIBx at 3 years.

Interestingly, in this study, there was no correlation between change in PSA over time and the likelihood of cancer detection. Men with stable PSA were just as likely to have cancer as those with a rising PSA. Of the 8 men found to have cancer, 4 underwent radical prostatectomy; all were found to have organ-confined disease. As such, the implication of this study is that men with HGPIN should undergo delayed biopsy at 3 years after the diagnosis. Such biopsies will result in a high likelihood of cancer detection and a low likelihood of allowing the disease to progress beyond a curable stage.

Updated data from our institution demonstrate that 22.9% of men with HGPIN are found to have prostate cancer on first delayed-interval biopsy at a median of 33.2 months. To date, a small subset of men has undergone a second DIBx at a mean of 31 months after the first DIBx. Twenty-five percent of these men were found to have prostate cancer. Overall, among men with HGPIN, there appears to be a

substantial cumulative risk for developing cancer over a period of 5 years after the initial diagnosis. As such, we have continued to recommend that our patients undergo DIBx every 2 to 3 years, as long as prostate cancer screening is clinically appropriate for those individuals.

## Prevention/Intervention Strategies for HGPIN

Because the long-term natural history of HGPIN, along with the average time to progression, is poorly defined, it is not well justified to use conventional treatments for prostate cancer in individuals with isolated HGPIN. As such, routine radical prostatectomy or radiotherapy in men with HGPIN is ill advised. Because it is unclear what percentage of men will develop prostate cancer, and the lead time to cancer development and ultimate prostate cancer mortality is likely very long, empiric treatment would likely result in significant overtreatment.

Despite the fact that the natural history of HGPIN remains poorly defined, it is clear that men with HGPIN are at a relatively high risk for developing prostate cancer. If, in fact, HGPIN represents the early end of the prostate cancer spectrum, then despite the prolonged lead time, patients with isolated HGPIN who are relatively young and without comorbidities are at an increased risk of prostate cancer death when compared with the whole population. As such, it remains extremely desirable to develop strategies for prevention and/or nontoxic therapeutic intervention in this cohort. In designed trials of chemopreventive agents, several have advocated the selection of men with HGPIN as the best high-risk group for study.

Critical in approaching the patient with HGPIN is the recognition that monitoring must be done histologically. HGPIN is not thought to contribute to PSA elevation,[26,27] which, along with the data demonstrating no correlation between change in PSA and likelihood of cancer on delayed-interval biopsy, illustrates that PSA alone cannot measure the therapeutic or preventive effect of a therapy targeting HGPIN. Similarly, the absence of HGPIN on follow-up biopsy tells one relatively little, given the risk of sampling error on repeat biopsy.[25] As illustrated previously, the use of extended biopsy has increased this risk through a resultant downward "stage migration" of HGPIN at the time of diagnosis. Clearly, the only valid end point in the evaluation of intervention for HGPIN is the frequency of cancer diagnosis at delayed follow-up.

Selection of agents for HGPIN intervention has largely been based on epidemiologic and biologic observations regarding prostate cancer. The majority of chemoprevention strategies for prostate cancer currently under study use dietary agents that have been observed to reduce prostate cancer incidence in longitudinally followed cohorts. Such agents are difficult to study because 1) they likely require long treatment periods to demonstrate clinical effect, 2) their dosing is poorly understood, 3) their absence from the diet of the control group is hard to ensure, and 4) although apparently effective in primary prevention among individuals at low risk, their role in preventing progression of HGPIN to cancer or of small cancers to larger cancers is completely untested. Thus, although biologically and epidemiologically intriguing, it is quite difficult to demonstrate a true therapeutic effect in a very high–risk group.

## Hormonal Therapy for HGPIN

In tailoring a treatment strategy for HGPIN, it seems more appealing to base it on the common biology of HGPIN and prostate cancer. A large body of evidence exists to suggest that, like prostate cancer, HGPIN is hormone responsive. Individuals pretreated with pharmacologic castration prior to radical prostatectomy are less likely to have HGPIN demonstrated on pathologic review.[28] Likewise, individuals treated with antiandrogens appear to have a reduction in detectable HGPIN.[29] As mentioned previously, the absence of HGPIN does not imply a lower risk in men with HGPIN previously diagnosed; however, in these cases, when compared with untreated controls, it does suggest a direct effect of hormone ablation on HGPIN itself.

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At present, 1 trial of an antiandrogen, hydroxyflutamide, in the treatment of HGPIN is under way. The strategy of using an antiandrogen is appealing because of the known effects of androgen deprivation on HGPIN and prostate cancer progression. Administration of hydroxyflutamide to transgenic mice of the TRAMP (transgenic adenocarcinoma of the mouse prostate) line (which normally rapidly develop prostate cancer) results in a delay in the onset and reduction in the prevalence of HGPIN and prostate cancer.[30]

Clearly, the major limitation of an antiandrogen in the treatment of HGPIN is the broad side-effect profile observed when interrupting the androgen axis. In addition to antiproliferative effects in the prostate, the use of such agents may result in changes in sexual function, muscle mass,

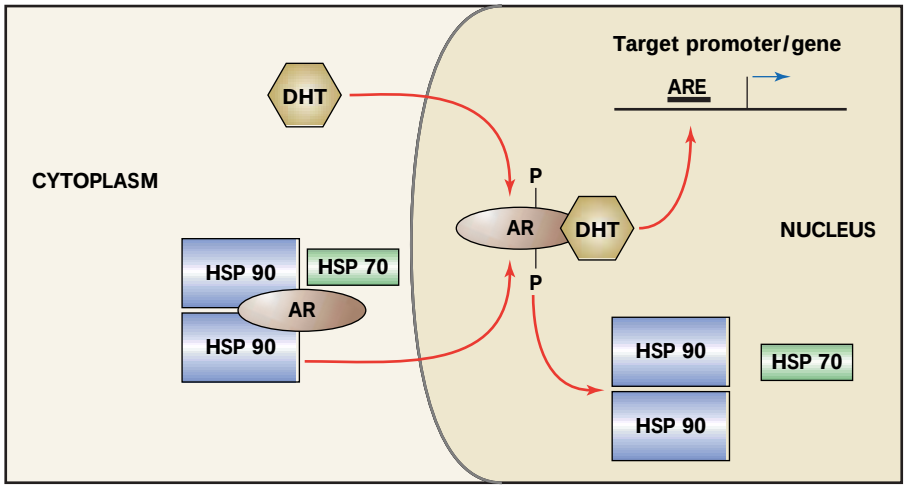



Figure 1. *On binding to a ligand, the androgen receptor (AR) disassociates from an inactive complex in the cytosol, translocates to the nucleus, and binds to the promoter sequence of target genes at the steroid response element. It is through activation and repression of target genes that steroids initiate programs of cell growth or differentiation. ARE, androgen response element; DHT, dihydrotestosterone; HSP, heat shock protein; P, promoter.*

body habitus, energy levels, breast size, breast sensitivity, and liver function. Collectively, although likely to have some impact on preventing cancer progression, the side-effect profile may affect ultimate patient compliance in an otherwise healthy population.

Finasteride, a 5α-reductase inhibitor, has received recent attention as a potential chemopreventive agent. In the Prostate Cancer Prevention Trial, 18,880 men with normal serum PSA and a normal prostate examination were randomized to placebo or finasteride. All men were offered end-of-study biopsy.[31] A 24.8% ($P < .0001$) reduction in cancer detection was seen among the finasteride-treated men. There are several concerns regarding the trial, including the relatively high rate of cancer detection overall, the sexual side effects, the fact that fewer men in the finasteride group underwent repeat biopsy ($P < .001$), and the higher incidence of cancers with Gleason scores $> 7$ observed in the treatment arm ($P < .001$).[31,32]

Although it is clear from this study that finasteride does lower the likelihood of prostate cancer, its use as a chemopreventive agent has not reached great popularity among practicing urologists. This is probably the result of the difficulty in interpreting the significance of finasteride's effect on tumor grade. An ongoing trial of dutasteride, another 5α-reductase inhibitor, will likely address this issue further. Given the efficacy of finasteride in prostate cancer chemoprevention, a study of its effects on HGPIN should be considered.

## Selective Estrogen Receptor Modulators as Prevention Agents

Most steroid receptors function by binding to ligands. When unbound, the receptors remain inactive with a protein complex. On binding to a ligand, the receptor takes on an active form, translocates to the cell nucleus, and regulates cellular function through directly binding to DNA to turn target genes on or off (Figure 1). This activation or repression of specific target genes results in cell responses such as growth or differentiation.

The biology of steroid receptors is defined by several variables, including the tissue type of the cell, the amount of ligand presented, the presence or absence of other ligands, and the competing effects of other steroid receptors. In the case of the estrogen receptor (ER), there are 2 well-described receptor subtypes: ER-α and ER-β.[33] Each receptor differs in its affinity for individual estrogens, its tissue distribution, and its cellular effects.

In the case of the prostate, ER-α is located mainly within the prostate stroma whereas ER-β is located predominantly within the epithelium.[34] Stimulation of ER-β with estrogens appears to result in an antiproliferative or differentiating effect in both benign and malignant prostate epithelium.[35] This observation has been exploited in developing chemoprevention strategies for prostate cancer using soy-based dietary supplements. Isoflavones, or soy-based estrogens termed phytoestrogens, which bind selectively to ER-β, are thought to represent the active ingredient responsible for lowering the incidence of prostate cancer among men eating soy-enriched diets.

The effects of ER-α on the prostate are more complex than those of ER-β. As detailed in a separate article in this supplement, animal studies demonstrate that androgens alone do not result in prostate cancer.[36] When combined with estrogens, however, androgens may result in prostate cancer. This suggests a necessary influence of estrogens in prostate cancer development and progression. It is believed that such an influence is exerted through stimulation of prostatic stroma, resulting in the production of growth factors that exert a growth-stimulatory effect on prostate epithelium and cancer cells. As such, stimulation of ER-α acts to "accelerate" prostate progression whereas ER-β acts to "brake" it.[35]

The use of diethylstilbestrol (DES) was popularized in the 1960s and

Table 3
Cancer Detection Among Transgenic Mice of the TRAMP Line Treated With Either Placebo or Toremifene*

| Drug | 20 wk, % | 25 wk, % | 30 wk, % |
|---|---|---|---|
| Placebo | 100 | 83 | 100 |
| Toremifene | 14 | 20 | 28 |

*Toremifene treatment results in a significant delay in the onset of prostate cancer as well as a reduction in the prevalence.
TRAMP, transgenic adenocarcinoma of the mouse prostate.
Data from Raghow S et al.[30]

1970s as a means of providing hormonal control of prostate cancer. Although DES binds to ER-α and -β, its predominant effect when used at clinical doses is to suppress the hypothalamic-pituitary axis, thus resulting in castrate testosterone levels. In the absence of testosterone, ER-α stimulation does not appear to have growth-stimulatory effects on prostate cancer. Although DES is potentially effective, the resultant pharmacologic castration, along with a relatively high incidence of cardiovascular complications, makes it an undesirable prevention agent.

Selective estrogen receptor modulators (SERMs) are synthetically derived estrogen receptor ligands that may have differing affinities or functional effects at the estrogen receptor subtypes.[37] Depending on the SERM, one may observe stimulation of both receptors, selective stimulation of one receptor, a greater degree of stimulation of one receptor than the other, or blocking of either receptor in combination with stimulation of the other. In addition, individual SERMs may exert differential effects on individual tissues of the body, depending on the ability of the bound receptor to activate target genes.

Toremifene is a SERM initially developed as an antiestrogen for the treatment of breast cancer. The agent showed antitumor activities similar to those of tamoxifen in preclinical studies of breast cancer. In clinical use, tamoxifen has been more widely used as an adjuvant agent in the treatment of breast cancer than has toremifene. Despite this, toremifene carries unique attributes, including a very favorable side-effect profile[38,39] and an efficacy similar to that of tamoxifen.[39] Clearly, the latter attribute is one that could be exploited in the treatment of prostate cancer. As ER-α appears to have a cancer-stimulatory effect on the prostate whereas ER-β has a cancer-suppressive effect, the selective inhibition of ER-α may offer a novel chemoprevention strategy.

## Toremifene in the Treatment of HGPIN

Given the strong rationale for use of a SERM in the preventive treatment of prostate cancer, preclinical studies were conducted in a transgenic animal model of prostate cancer.[30] The TRAMP line animals, expressing the SV40 T antigen in a prostate-specific fashion, normally develop HGPIN and subsequent prostate cancer relatively rapidly. Animals were treated with increasing doses of toremifene. Animals treated with toremifene had a reduction in the incidence of prostate cancer and a significant delay in its onset. Tumors developed by week 17 in placebo animals but not until week 29 in animals treated with low-dose toremifene (Table 3).

Several interesting observations were made from the preclinical data with toremifene. First, whereas placebo animals were routinely found to have HGPIN, those treated with toremifene had none. Second, the effect of toremifene on prostate carcinogenesis was greatest at lower doses. Although this seems contrary to traditional dosing of anticancer agents, which seeks the maximum tolerated dose, it is postulated to reflect a more preferential binding of toremifene to ER-β at lower doses. Finally, the efficacy of toremifene exceeded that of hydroxyflutamide, suggesting that despite the fact that toremifene does not directly influence the androgen receptor, its effect on prostate cancer growth and

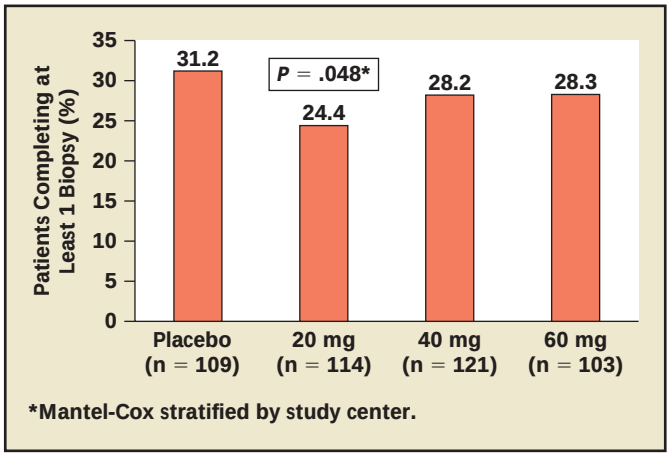



Figure 2. *Comparison of overall cancer incidence on follow-up biopsy between men treated with placebo and those given increasing doses of daily toremifene. A significant reduction in cancers diagnosed was observed among men treated with 20 mg of toremifene daily. Data from Steiner MS et al.*[41]

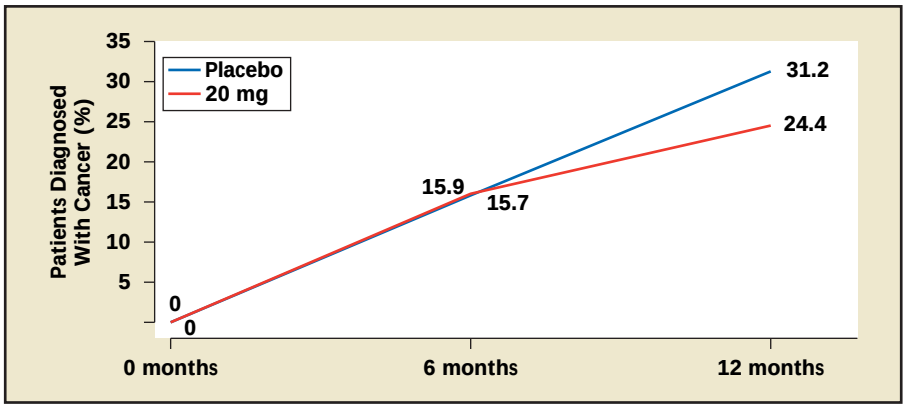



Figure 3. *A depiction of cancer diagnosis on serial biopsy among men treated with placebo or 20 mg toremifene daily. Although the incidence of cancer did not differ between groups at 6-month biopsy, a 48.2% reduction in cancer diagnosis among men treated with 20 mg of daily toremifene was observed at 12-month biopsy. Data from Steiner MS et al.*[41]

progression may be greater than that of agents that do.

Based on the promising findings of the preclinical studies of toremifene in prostate cancer prevention, a phase IIa trial was conducted in men with HGPIN. A total of 21 men with HGPIN diagnosed within 6 months of enrollment were treated with 60 mg/d of toremifene.[40] Repeat biopsy was conducted after 4 months of treatment. Of men completing therapy, 72% were found to have no evidence of HGPIN on repeat biopsy. This was believed to represent a reduction in the incidence of HGPIN, although no control group was available for comparison.

Despite an apparent reduction in the incidence of HGPIN on follow-up biopsy, the men's PSA levels increased presumably as a result of a secondary effect of estrogen receptor blockade. By blocking estrogen receptors in the hypothalamus, the body perceives systematic estrogen and, therefore, testosterone levels to be low. The result is an increase in luteinizing hormone–releasing hormone, luteinized hormone, and testosterone production. An increase in circulating testosterone likely results in increased PSA expression by prostate cells. Alternatively, growth inhibitory or differentiating effects on prostate epithelium may also result in an increase in serum PSA levels. The important "take-home" message is that in following men treated with toremifene, an increase in PSA level is expected and may not reflect an increased risk of prostate cancer.

An important observation of the phase IIa study of toremifene was the recognition that the presence or absence of HGPIN likely could not serve as an adequate end point for evaluation of the chemopreventive potential of the drug. As such, the investigators embarked on a multicenter phase IIb dose-finding study of toremifene in the treatment/prevention of HGPIN using prostate cancer on follow-up biopsy as a primary end point.[41] A total of 514 men with a history of diagnosed HGPIN were randomized to placebo or 1 of 3 escalating doses of toremifene: 20, 40, and 60 mg. Repeat biopsies were carried out at 6 and 12 months using a minimum of 8 cores. The incidence of prostate cancer on follow-up biopsy was compared between groups.

A total of 31.2% of men in the placebo group were found to have prostate cancer on follow-up biopsy.[41] A reduction in prostate cancer incidence by 1 year of follow-up was observed among patients treated with 20 mg of toremifene. The incidence of prostate cancer on follow-up was 24.4%, 28.2%, and 28.3% among men treated with 20, 40, and 60 mg of toremifene, respectively (Figure 2). As in the preclinical model, the most marked reduction in cancer was seen in the lowest-dose group. Only the 20 mg group reached statistical significance in cancer reduction ($P = .048$).

When evaluating the cancer incidence on follow-up, it is interesting to note that no significant difference in cancer detection was seen at the 6-month biopsy (Figure 3). This may partly be the result of the presence of preexisting occult cancers but also may reflect the variable mix of the patients included with regard to

Figure 4. *Comparison of cancer incidence on 1-year follow-up biopsy between men treated with placebo and those given increasing doses of toremifene. A significant reduction in cancers diagnosed was observed among men treated with 20 mg of toremifene daily. CMH, Cochran-Mantel-Haenszel. Data from Steiner MS et al.*[41]

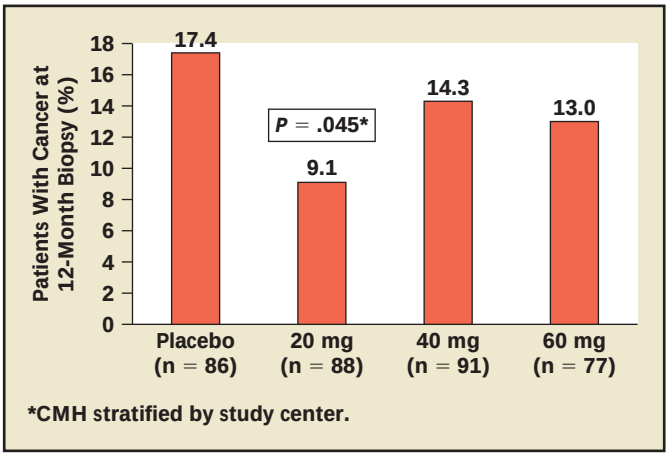


Table 4
Gleason Score Distribution Among Men Diagnosed With Cancer While Being Treated With Increasing Doses of Toremifene*

| | Placebo | 20 mg | 40 mg | 60 mg |
|---|---|---|---|---|
| % of cancer in men with Gleason scores ≥ 7 | 24 (8 of 33) | 26 (7 of 27) | 12.5 (4 of 32) | 17 (5 of 29) |
| % men biopsied with Gleason scores ≥ 7 | 7.4 | 6.1 | 3.3 | 4.7 |

*No discernible difference in the number of high-grade cancers is identified.
Data from Steiner MS et al.[41]

sampling prior to inclusion. As demonstrated in historical series, lesser baseline sampling will increase the likelihood of cancer diagnosis on immediate repeat biopsy. As such, within this phase IIb study of toremifene, the results of 12-month biopsy (and further delayed biopsy) may be most useful in determining the preventive efficacy of the drug.

When comparing the 12-month biopsies only, a 48.2% reduction in cancer incidence was observed in the 20 mg–treated group compared with the placebo group (Figure 4). Interestingly, the likelihood of detected cancer among the placebo-treated group increased at the 12-month biopsy relative to the 6-month biopsy (Figure 3). If one were to conclude that all cancers detected at 12 months were occult preexisting cancers, then the likelihood of cancer should decrease on each serial sampling. One could, therefore, cautiously conclude that a reduction in cancer incidence at 12-month follow-up biopsy is representative of prevention of HGPIN progression to prostate cancer. Clearly, further delayed follow-up biopsies would be helpful in strengthening this belief.

Interestingly, individuals diagnosed with prostate cancer while receiving toremifene were not more likely to have high-grade disease than those treated with placebo (Table 4). This finding differs from that of the Prostate Cancer Prevention Trial, in which cancers diagnosed during finasteride treatment were higher grade than those diagnosed during placebo treatment. Admittedly, the toremifene treatment period was short, and it may be too early to reliably determine the effect of the drug on tumor biology, but the finding does reassure the urologist that SERM therapy may be safer than antiandrogen therapy while being similarly efficacious. Long-term data are required to validate this as well.

In evaluating toxicity, the overall incidence of adverse events was quite low in both the placebo and toremifene groups.[42] Serious adverse events were reported in 11% of placebo-treated patients and 7% of men treated with 20 mg of toremifene. The most commonly reported side effects among toremifene-treated patients include headache, urinary frequency, fatigue, nocturia, and arthralgia. Hot flashes, decreased libido, and erectile dysfunction were relatively infrequent (Table 5). The

Table 5
Distribution of Toxicities Observed While Being Treated With Increasing Doses of Toremifene

| Adverse Event | Placebo, % (n = 130) | 20 mg, % (n = 125) | 40 mg, % (n = 134) | 60 mg, % (n = 125) | All Subjects, % (n = 514) |
|---|---|---|---|---|---|
| Headache | 10 | 10 | 6 | 11 | 9 |
| Urinary frequency | 10 | 6 | 7 | 6 | 8 |
| Fatigue | 4 | 8 | 7 | 8 | 7 |
| Nocturia | 5 | 5 | 8 | 8 | 7 |
| Arthralgia | 5 | 5 | 8 | 6 | 6 |
| Dizziness | 2 | 8 | 8 | 4 | 5 |
| Hot flashes | 5 | 4 | 8 | 4 | 5 |
| Urinary urgency | 6 | 6 | 3 | 6 | 5 |
| Nasopharyngitis | 3 | 6 | 6 | 4 | 5 |
| Nausea | 5 | 2 | 7 | 4 | 5 |
| Constipation | 4 | 4 | 4 | 6 | 4 |
| Erectile dysfunction | 4 | 3 | 5 | 6 | 4 |
| Urinary retention | 3 | 3 | 7 | 5 | 4 |
| Urinary flow decrease | 5 | 2 | 5 | 4 | 4 |
| Insomnia | 5 | 2 | 3 | 6 | 4 |
| Libido decrease | 3 | 1 | 6 | 5 | 4 |

*No substantial difference is noted between patients treated with toremifene and those treated with placebo.
Data from Steiner MS et al.[42]

incidence of any of these side effects did not differ from the placebo arm.

Criticisms of the phase IIb data include the lack of a standardized biopsy schema, potentially resulting in undersampling at earlier biopsies and oversampling in some centers using a more extended sampling regimen. The relative equivalence of cancer detection rates in the 4 study groups at 6-month biopsy suggests that the biopsy schema is relatively similar, and perhaps suggests that the randomization among centers is good as well. An additional concern is the relatively high rate of detection at the 12-month biopsy. One might expect that individuals would have a decline in cancer detection given the extensive sampling up to that point. Whether 1 year of follow-up is an adequate time period for HGPIN to progress to cancer remains to be validated in further prospective cohorts. A planned phase III trial of toremifene in the treatment of HGPIN will give the opportunity to validate the findings.

Based on the promising nature of the phase IIb trial outcome, a phase III trial of 20 mg toremifene versus placebo in men with HGPIN will soon be under way. The study is a planned trial of 1200 men. The inclusion criteria have been altered to include only men with a negative minimum 10-core biopsy at baseline. The added effect of this will be to remove occult cancers at baseline. Additionally, unlike the phase IIb study, biopsies will be performed at 12 and 18 months of treatment, allowing observation of more delayed outcomes.

## Conclusion

HGPIN is a precursor to prostate cancer found as an isolated entity at prostate biopsy in a growing subset of men. Such men are believed to be at an increased risk of both coexisting prostate cancer at baseline and cancer progression at a delayed interval. Monitoring of these patients should include sampling with a minimum of 12 cores at baseline and a delayed-interval biopsy every 2 to 3 years after the initial diagnosis. The absence of rise in serum PSA does not predict a lower likelihood of prostate cancer on delayed-interval biopsy, as PSA is a poor means of monitoring HGPIN. Rising PSA in men with isolated HGPIN may necessitate an earlier biopsy as it may suggest an unsampled coexisting prostate cancer.

Because of the clearly higher risk of progression to prostate cancer in men with HGPIN, these patients represent an ideal high-risk cohort in whom to target prostate cancer preventive and therapeutic agents. Therapeutic agents are more likely to be efficacious as a

### Main Points

- Prevention as a therapeutic approach to prostate cancer is appealing because of 1) the significant concern regarding overtreatment of early cancers, 2) the difficulty in defining metastatic potential at an early point in the disease's natural history, and 3) the variability in disease phenotype at later stages.
- Men with high-grade prostatic intraepithelial neoplasia (HGPIN) have a high risk of occult malignancy as well as a risk of progression to prostate cancer at a delayed interval. As such, individuals with isolated HGPIN may represent the best example of men in whom the progression to prostate cancer has begun and appear to be ideal candidates for prevention strategies.
- The parallel distribution of HGPIN and cancer, along with the temporal relationship, strongly implicates HGPIN as a precursor to invasive prostate cancer.
- The high rate of HGPIN prevalence among radical prostatectomy specimens predicts a high likelihood of coexistent cancer when HGPIN is found on routine biopsy. Even in individuals with no cancer identified on repeat biopsy, the clinician should have a strong suspicion of undiagnosed foci of microscopic cancer.
- If HGPIN represents the early end of the prostate cancer spectrum, then despite the prolonged lead time, patients with isolated HGPIN who are relatively young and without comorbidities are at an increased risk of prostate cancer death when compared with the whole population. Therefore, there is a need to develop strategies for prevention and/or nontoxic therapeutic intervention in this cohort.
- A large body of evidence exists to suggest that, like prostate cancer, HGPIN is hormone responsive.
- Because estrogen receptor (ER)-$\alpha$ appears to have a cancer-stimulatory effect on the prostate whereas ER-$\beta$ has a cancer-suppressive effect, the selective inhibition of ER-$\alpha$ may offer a novel chemoprevention strategy.
- Study data suggest that toremifene is extremely well-tolerated in men with HGPIN, reduces the likelihood of HGPIN on follow-up biopsies, slightly increases the serum PSA without increasing the likelihood of prostate cancer, lowers the likelihood of progression to prostate cancer at a dose of 20 mg/d, and has no effect on tumor grade at the time of diagnosis.

single intervention when used earlier in the natural history of prostate cancer because of 1) a more homogeneous cell population, 2) a lower disease volume, and 3) a reduced virulence of the individual cell. To date, chemoprevention strategies in prostate cancer have used either dietary agents or agents that block the effect of androgens on the prostate. Such studies have rarely been targeted to the HGPIN population, but in evaluating the therapeutic strategy, they have suffered from difficulty in assessing short-term outcomes because of the nature of the intervention or the unacceptably high toxicity for a preventive agent.

Given the provocative evidence that estrogens play an essential role in the development and progression of prostate cancer, SERMs represent an exciting alternative to drugs targeting the androgen axis in prostate cancer prevention. SERMs act to selectively block or stimulate estrogen receptor subtypes, depending on the individual tissue in which they are expressed. Toremifene, an antiestrogen developed for breast cancer therapy, represents a SERM capable of selectively blocking ER-$\alpha$ in the prostate at low doses. As such, a good rationale exists for the use of toremifene in the treatment of patients with HGPIN.

To date, phase IIa and IIb data suggest that toremifene 1) is extremely well-tolerated in men with HGPIN, 2) reduces the likelihood of HGPIN on follow-up biopsies, 3) slightly increases the serum PSA without increasing the likelihood of prostate cancer, 4) lowers the likelihood of progression to prostate cancer at a dose of 20 mg/d, and 5) has no effect on tumor grade at the time of diagnosis. At a 20 mg dose, toremifene reduces the likelihood of prostate cancer by 48.2% on 1 year delayed-interval biopsy and by 21.8% overall. Collectively, these data represent the most appealing strategy for prostate cancer prevention to date. Based on the findings of the phase II studies, a large randomized phase III study of toremifene in men with HGPIN is planned. ■

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