Androgen Deprivation as a Strategy for Prostate Cancer Chemoprevention

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Androgens are required for the normal development and function of the prostate gland. Prostate cancer and benign prostatic hyperplasia are common in men and develop in an environment of continuous androgen exposure. The utility of androgen deprivation as a treatment for advanced prostate cancer was first demonstrated in 1941 (1), and many new classes of drugs that interfere with androgen production and function have been introduced in recent years. These agents are effective in treating prostate cancer and benign prostatic hyperplasia and may have an important role in chemoprevention.

Since 1991, prostate cancer has been the most common noncutaneous cancer and the second leading cause of cancer-related death in men. The major difficulty in treating prostate cancer is the limitation of current tools to accurately predict the behavior of a given tumor. Although many prostate cancers are clinically insignificant and will have an indolent course, others will result in considerable morbidity and mortality. The major dilemma with regard to prostate cancer is determining what men to treat and who would be better served by expectant management (2).

Previous efforts (3) have concentrated on treating invasive cancer, often in advanced stages. Other work (4,5) suggests that an evolving multistep molecular and cellular process, known as carcinogenesis, begins years before invasive cancer is detected. Chemoprevention refers to prevention of cancer or reduction of risk in susceptible individuals by administration of natural or synthetic drugs with little or no toxicity that suppress, delay, or reverse carcinogenesis (6,7). Chemoprevention is most effective in the early stages of cancer formation when reversibility may be feasible. In prostate carcinoma, the time from tumor initiation and progression to invasive carcinoma often begins in men in the fourth and fifth decades of life and extends across decades, allowing sufficient time to halt or to reverse carcinogenesis (8,9).

Why Chemoprevention?

The utility of prevention of disease as a means of improving quality of life and outcome has been amply demonstrated in recent years; one of the first examples was the identification of atherosclerosis as the causative mechanism for cardiovascular disease (10). Improved understanding of atherosclerosis resulted in important health initiatives, including modifications of lifestyle, diet, and tobacco usage and introduction of cholesterol-lowering, antihypertensive, and antiplatelet agents that have favorably affected life expectancy by reduction of cardiovascular risk (4,10). Similar preventive strategies are being developed to suppress the process of carcinogenesis. In chemoprevention of prostate cancer, as with prevention of cardiovascular disease, the potential public health implications are substantial.

Antioxidant vitamins often have beneficial effects in prevention and treatment of cancer, according to results from chemoprevention trials. Daily treatment with high doses of isotretinoin, a vitamin A derivative (retinoid), is effective in preventing second primary tumors in patients who have been treated for squamous cell carcinoma of the head and neck (11). Administration of vitamin E and several retinoid agents results in clinical and histologic regression of premalignant oral lesions (12).

Sulindac, a nonsteroidal anti-inflammatory drug, significantly decreased mean colonic polyp number and diameter in patients with Gardner’s syndrome and familial polyposis (13-17). Tamoxifen, an antiestrogen, exhibits potent activity against hormone-sensitive forms of breast cancer and is currently being evaluated in a phase III clinical trial in women at high risk for breast cancer (18).

For prostatic carcinoma, the interval between tumor initiation and progression is measured in decades. Autopsy studies indicated that prostatic intraepithelial neoplasia, the precursor of most prostate cancers, precedes carcinoma by 10 years or more, first emerging in men in the third decade of life (8,19,20). There may be sufficient time to halt or reverse carcinogenesis. Absolute eradication of precursor lesions or early cancer may not be required for the strategy to have a beneficial effect, because a delay in the development or slowing the progression of prostatic carcinogenesis may prolong a patient’s life.

Why Androgen Deprivation?

The prostate gland requires androgens for proper growth, maintenance, and function. Men with 5α-reductase deficiency (21,22) and men castrated when young (eunuchs) do not develop prostate cancer (23). These populations provide indirect evidence that a strategy directed toward interrupting or decreasing...
exposure to androgens can significantly decrease prostate cancer incidence.

Androgen-deprivation therapy causes marked and characteristic changes in the normal prostate and in prostate cancer (24). Ferguson et al. (25) reported a marked decrease in the prevalence and extent of high-grade intraepithelial neoplasia in prostates after androgen-deprivation therapy compared with untreated prostates. This decrease was accompanied by epithelial hyperplasia, cytoplasmic clearing, and prominent acinar atrophy, with a decreased ratio of acini to stroma. These findings indicate that the dysplastic prostatic epithelium is hormone dependent. In the normal prostatic epithelium, luminal secretory cells are more sensitive to the absence of androgens than are basal cells, and these results show that the cells of high-grade prostatic intraepithelial neoplasia share this androgen sensitivity. The loss of normal, hyperplastic, and dysplastic epithelial cells with androgen deprivation is probably from acceleration of programmed single-cell death (apoptosis) with subsequent exfoliation into acinar lumina (26,27).

Prostatic epithelium from benign hyperplasia and from most carcinomas responds to hormonal manipulation. This finding suggests that the process of prostatic carcinogenesis can be favorably modulated if an appropriate agent and treatment regimen can be determined. Intervention early in carcinogenesis may be more successful in improving survival because the burden of affected cells is low. Once stromal invasion occurs, it may be too late to prevent further disease progression (10). Agents capable of producing effective and reversible androgen-deprivation therapy are now available, and chemoprevention of prostate cancer is a realistic possibility (28).

Selection of a Suitable Androgen-Deprivation Chemopreventive Agent

Surgical castration and most chemical agents capable of effective androgen-deprivation therapy are associated with some degree of significant adverse effects. These effects are often acceptable to patients with cancer, but not to a healthy population of men in whom the risk of developing cancer is relatively low. Patients with high-grade prostatic intraepithelial neoplasia or other high-risk target populations are more likely to accept minor side effects if the chemopreventive effort is short term, efficacious, and inexpensive and has the potential for significant improvement in long-term outcome (18,29). Chemoprevention must match potential side effects to degree of cancer risk (30).

Hormonal Agents

Estrogen therapy with diethylstilbestrol lowers luteinizing hormone concentration and thereby depresses serum testosterone level (31). Diethylstilbestrol in doses of 3 mg/day or more results in significant cardiovascular toxicity (32). Diethylstilbestrol at 1 mg/day has fewer side effects but does not reliably reduce testosterone concentration to castrate levels (33). Other than cardiovascular complications, estrogens have been associated with fluid retention, gynecomastia (32), and loss of libido and potency (34)—side effects that probably outweigh any chemopreventive benefit of these agents.

Luteinizing Hormone-Releasing Hormone Analogues

Continuous administration of high doses of luteinizing hormone-releasing hormone analogues inhibits the release of luteinizing hormone and follicle-stimulating hormone and subsequently suppresses testosterone, reaching castrate levels after 3-4 weeks. Luteinizing hormone-releasing hormone analogues (leuprolide acetate and goserelin acetate), however, initially produce a significant increase in testicular androgen production, known as the flare reaction, which can be inhibited with antiandrogens. The major side effects of these agents include impotence, loss of libido, atrophy of muscles and the reproductive organs, and hot flashes. These potent agents are not suitable for chemoprevention in the general population; however, in high-risk target populations such as those with high-grade prostatic intraepithelial neoplasia, perhaps 3-6 months of therapy could significantly improve outcome and outweigh the side effects incurred during the treatment interval.

5α-Reductase Inhibition

The 5α-reductase enzyme is a membrane-bound protein dependent on the reduced form of nicotinamide–adenine dinucleotide phosphate and is responsible for conversion of testosterone to the more potent dihydrotestosterone in androgen-dependent target cells (35). Dihydrotestosterone has a greater affinity than testosterone for the androgen receptor, and it is thought to actively modulate prostatic growth. Finasteride is a steroid analogue that acts as a competitive and specific inhibitor of 5α-reductase, resulting in suppression of serum and intraprostatic dihydrotestosterone concentrations to castrate levels, with subsequent reduction in prostatic size. 5α-Reductase inhibition results in a significant increase in intraprostatic testosterone levels, allowing testosterone-mediated functions including libido, potency, and male musculature to remain largely unaffected (35). Finasteride is approved for treatment of symptomatic benign prostatic hyperplasia (36). It is associated with a 50% reduction in prostate-specific antigen levels (37,38), which is significantly lower than the reduction associated with medical or surgical castration (39). The role of finasteride in the treatment of human prostate cancer or its precursor lesions is unknown. Currently, other 5α-reductase inhibitors are in development (e.g., episteride). Tumor growth has been suppressed by 5α-reductase inhibition in animal and human tumor cell lines (31,40,41). An attractive feature of finasteride is its excellent safety profile (42), making it a reasonable candidate for chemoprevention trials in the general and high-risk target populations.

Nonsteroidal Antiandrogens

Nonsteroidal antiandrogens competitively bind to androgen receptors at the target cell level. This class of agents blocks testicular and adrenal androgens. Antiandrogens are currently approved (e.g., flutamide and bicalutamide) for use in combination therapy with a luteinizing hormone-releasing hormone analogue for complete androgen blockade (43,44) in the management of prostate cancer. Antiandrogens and 5α-reductase inhibitors, if used alone or in combination for chemoprevention, may offer a quality-of-life advantage over other androgen ablation methods because they do not reduce serum testosterone levels and therefore do not have a marked inhibitory effect on libido and potency (43,45).

Flutamide and bicalutamide are nonsteroidal antiandrogens that selectively inhibit androgen receptors, including those in the
creases in serum testosterone levels have been noted (46,47). These agents have no androgenic or progestational activity and are able to effectively counteract testicular and adrenal androgens. When flutamide or bicalutamide has been used as monotherapy for prostate cancer, mild increases in serum testosterone levels have been noted (47,48). The increase in serum testosterone levels with flutamide administration appears to be clinically insignificant, showing no association between testosterone levels and patient response to treatment (48).

Flutamide is approved at a dose of 250 mg given three times a day at 8-hour intervals for combination therapy with a luteinizing hormone-releasing hormone analogue for treatment of prostate cancer. Flutamide has been evaluated at this dose to determine its long-term efficacy as monotherapy for prostate cancer (46). Adverse effects in this population included diarrhea, gynecomastia, nausea or vomiting, hepatitis, vertigo, and hot flashes (46). A reduction in dose (e.g., flutamide at 250 mg given once daily or 125 mg given two or three times daily) may offer chemopreventive efficacy and minimize or eliminate many adverse effects.

Combination Therapy

Combining androgen-ablation agents may decrease prostate cancer risk in target populations such as those with high-grade prostatic intraepithelial neoplasia. Combination therapy may decrease overall side effects by lowering effective doses and shortening treatment durations. A nonsteroidal antiandrogen agent could be used in combination with a 5α-reductase inhibitor in men who want potency preserved (34,45). Combination therapy (49) with a luteinizing hormone-releasing hormone analogue and an antiandrogen would be an option for men in whom potency is not a concern.

Surrogate End-Point Biomarkers

Recently, the National Cancer Institute sponsored workshops to design clinical trial strategies for chemoprevention and introduced the concept of surrogate end-point biomarkers as intermediate trial end points. Intermediate trial end points include histologic and biochemical alterations, proliferation, differentiation, and genetic biomarkers (Table 1) (50). Each of these end-point biomarkers is measured in serum or tissue specimens, such as formalin-fixed, paraffin-embedded, needle biopsy specimens, and may be modifiable by intervention. The problem of the measurement of these biomarkers during clinical trials in humans is the amount of tissue available for analysis. Recent advances in the development of immunohistochemistry, in situ hybridization (51), and other microassay techniques make such measurements feasible on serial sections of needle biopsy specimens of the prostate. Chemoprevention trials may apply these techniques to study the multistep process of carcinogenesis and to determine the cellular effects of potential chemopreventive agents on surrogate end-point biomarkers. A significant limitation of monitoring surrogate end-point biomarkers from sequential prostate needle biopsies is the inability of current techniques to reliably resample the same microscopic focus after chemopreventive therapy to determine if the intervention was efficacious. In a solid organ such as the prostate, this limitation is unresolvable.

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<tr>
<th>Table 1. Potential surrogate end-point biomarkers for prostate cancer chemoprevention clinical trials</th>
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<td>Histologic premalignant lesions</td>
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<td>High-grade prostatic intraepithelial neoplasia</td>
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<td>Biochemical markers</td>
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<td>Prostate-specific antigen</td>
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<td>Morphometric markers</td>
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<td>Nuclear DNA content (ploidy)</td>
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<td>Oncogene c-erbB-2 (Her-2neu) expression</td>
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<td>Fluorescence in situ hybridization for chromosome 8</td>
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<td>Reverse transcription–polymerase chain reaction for cells expressing prostate-specific antigen in serum</td>
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<td>Differentiation markers</td>
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<td>Microvessel density</td>
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Studies using cancer as an end point must treat large groups of subjects, recognizing that cancer will develop in only a small number early in the course of study. The number of subjects required in studies using surrogate end-point biomarkers is much fewer than in studies in which cancer incidence is the primary end point (52). Rather than having to wait many years to accumulate sufficient numbers of subjects with invasive cancer to determine if the intervention was successful, surrogate end points shorten the duration of chemoprevention trials (53). The smaller number of subjects and shorter duration of study are associated with a significant reduction in the cost of conducting chemoprevention studies (52). Agents that favorably modulate surrogate end-point biomarkers are reasonably likely to slow or reverse carcinogenesis, but their clinical utility must ultimately be validated by demonstrating a reduction in cancer incidence rates (54).

Target Populations for Prostate Cancer Chemoprevention

There are several target populations who can be considered for prostate cancer chemoprevention (Table 2). Two of these trial design strategies include patients diagnosed with cancer and can be considered “chemoactive” trials (55). These studies may provide information regarding the effectiveness of proposed agents on surrogate end-point biomarkers, premalignant lesions, and cancer. Trials using agents that affect prostate-specific antigen may need to consider masking these results from the patient and his treating physician during the study to avoid bias.

General Population (Normal Risk of Developing Prostate Cancer)

Chemoprevention clinical trials designed for the general population (normal risk) may require a relatively long time for cancer to develop in sufficient numbers of subjects. Prostate cancer is generally slow growing; thus, the period of study may be significantly longer and the number of subjects required comparatively higher than those in studies focusing on high-risk target populations. The major advantage of studies designed for
the general population is that the results are directly applicable to this group.

A large-scale national prostate cancer chemoprevention trial began a few years ago. The Prostate Cancer Prevention Trial is a randomized, double-masked, placebo-controlled, phase III trial of finasteride in the prevention of prostate cancer. This study has randomly assigned 18,000 men to receive either 5 mg of finasteride or placebo daily for 7 years, with a 3-month enrollment period during which all participants received placebo before treatment randomization. The trial opened on October 18, 1993, and completed enrolling patients in 1996 (36,36). Eligible subjects are men 55 years old or older with normal results upon digital rectal examination and prostate-specific antigen concentration less than 3 ng/mL; these subjects are stratified within each arm according to age, race, and history of first-degree relative with prostate cancer (36). The strict inclusion criteria should minimize the chance of enrolling men with existing prostate cancer. The primary end point of the Prostate Cancer Prevention Trial is the prevalence of prostate cancer at 7 years. Prostate cancer rates in each group will be established by biopsy of all subjects at 7 years or by the diagnosis of prostate cancer any time before that (36).

Results from a study of this magnitude should determine if finasteride significantly inhibits prostate cancer and what its role is as a chemopreventive agent; however, such a study also demonstrates that relying on cancer incidence as an end-point marker has various feasibility problems, including the requirement of a large number of participants, long duration of follow-up, and high costs (57). The relatively small risk of prostate cancer death in the general population limits the spectrum of chemopreventive agents capable of being tested, because few men at minimal risk would be willing to accept any degree of adverse effects for a reduction in risk of prostate cancer death (31).

Men at High Risk of Developing Prostate Cancer

Prostate cancer chemoprevention trials directed at African-American men or men with a strong familial predisposition for prostate cancer could potentially include highly motivated target populations. African-American men have the highest rates of prostate cancer in the world. Familial predisposition for early-onset prostate cancer probably accounts for about 9% of cases, and risk increases as the number of affected relatives increases (55,58). A man’s risk is twofold higher if a first-degree relative, such as a father or brother, has prostate cancer. The risk is fivefold to 11-fold higher if the man has multiple first-degree relatives with prostate cancer (55). Heredity appears to be an important risk factor for prostate cancer (58-60).

Men With High-Grade Prostatic Intraepithelial Neoplasia

High-grade prostatic intraepithelial neoplasia is a histopathologic finding considered to be the precursor of most prostate cancers (20). This lesion represents the putative precancerous end of the morphologic continuum that culminates in high-grade intraepithelial neoplasia and early invasive cancer (Fig. 1). Prostatic intraepithelial neoplasia is characterized by basal cell layer disruption, progressive loss of secretory differentiation markers, increased nuclear and nucleolar abnormalities, increasing proliferation potential, and increasing variation in DNA content (aneuploidy) (61). It is divided into low grade and high grade to replace the previous three-grade system (1 is considered low grade; 2 and 3 are considered high grade).

The incidence of prostatic intraepithelial neoplasia seems to increase with patient age. In an autopsy study of 152 young male patients aged 10-49 years, Sakr et al. (8) found the onset of disease in men in their third and fourth decades of life (9% and 20%, respectively), which preceded the onset of carcinoma by more than 10 years. The majority of cases were low grade; high-grade cases were first identified in the fifth decade. In the series by Sakr et al. (8), all five high-grade cases occurred in prostates containing carcinoma.

The clinical significance of recognizing prostatic intraepithelial neoplasia is based on its strong association with prostate cancer. Biopsy is the only definitive method for detecting this premalignant lesion and early invasive cancer. High-grade prostatic intraepithelial neoplasia is encountered in up to 16% of the general population limits the spectrum of chemopreventive agents capable of being tested, because few men at minimal risk would be willing to accept any degree of adverse effects for a reduction in risk of prostate cancer death (31).

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cell layer is disrupted. Note that the dysplastic changes occur in the superficial (luminal) secretory cell layer, perhaps in response to luminal carcinogens. Disruption of the basal cell layer accompanies the architectural and cytologic features of high-grade prostatic intraepithelial neoplasia and appears to be a necessary prerequisite for stromal invasion. The basement membrane is retained with high-grade prostatic intraepithelial neoplasia and early invasive carcinoma. From Bostwick DG, Brawer MK. Prostatic intra-epithelial neoplasia and early invasion in prostate cancer. Cancer 1987;59:788-94. Copyright 1987 American Cancer Society. By permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

grade intraepithelial neoplasia, patient age, and levels of pro-
state-specific antigen in sera were all significant predictors of
cancer, but prostatic intraepithelial neoplasia provided the high-
est risk ratio (14.9). Other investigators (63) have also reported
a high predictive value of prostatic intraepithelial neoplasia for
cancer, ranging from 38% to 100%. The high risk of cancer on
subsequent biopsy and the lack of treatment options (other than
watchful waiting and active surveillance) for patients with this
premalignant lesion provide a reasonable rationale for attempt-
ing chemoprevention efforts in this target population.

Cancer Patients Who Are Waiting for Radical Prostatectomy

Short-term treatment of men with biopsy-proven prostate
cancer by use of potential chemopreventive agents before radical prostatectomy may be the most practical and feasible clinical method to assess modulation of high-grade prostatic intraepithelial neoplasia and other potential surrogate end-point biomarkers (Fig. 2, A). The delay before radical surgery can be as long as several months, ample time for androgen-deprivation agents and other compounds to reach and maintain their appropriate blood and tissue levels. The entire radical prostatectomy specimen would then be available for study of the effect of the compounds on morphologic, biochemical, and genetic intermediate markers.

In a retrospective case–control study of preoperative andro-
gen-deprivation therapy, Ferguson et al. (25) found that therapy
caused a significant decrease in the prevalence and extent of
high-grade prostatic intraepithelial neoplasia in radical pros-
tectomy patients compared with untreated control subjects.
Similar studies could be performed prospectively as randomized,
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Patients With Early Prostate Cancer Treated by Watchful Waiting

Watchful waiting (active surveillance) is appropriate manage-
ment for some patients with prostate cancer, although the selec-
tion criteria for such patients remain a source of disagreement
(34,55). Most men who have prostate cancer will die with their
cancer rather than of their cancer. Investigators are attempting to
establish criteria for identifying patients with clinically signifi-
cant cancer (2). Preoperative determination of tumor volume is
difficult and too imprecise for individual patients to allow strati-
fication of therapy on this basis. Nonetheless, refinements in
preoperative assessment of prostate cancer extent and biologic
potential will allow some patients to be followed expectantly;
furthermore, the level of serum prostate-specific antigen has
emerged as a valuable surrogate for tumor growth and progres-

Modulation of High-Grade Prostatic Intraepithelial Neoplasia With
Androgen-Deprivation Therapy as a Strategy for Prostate Cancer Chemoprevention Trials

Premalignant lesions such as high-grade prostatic intraepithe-
lial neoplasia identify patients at high risk of developing inva-
sive cancer, and these patients are ideal target populations for
chemoprevention trials. The most efficient strategy for develop-
ing a chemoprevention program may be to perform two clinical trials concurrently, each based on the modulation of high-grade prostatic intraepithelial neoplasia but in different target populations. In patients with high-grade intraepithelial neoplasia associated with prostate cancer, a prospective, double-masked, placebo-controlled, chemoactive pilot study designed to measure the response of a potential chemopreventive agent in the period (3-6 weeks) before radical prostatectomy could be performed easily (Fig. 2, A). Androgen-deprivation therapy is commonly used in this population to downsize the prostate before radical prostatectomy. This study would determine the response of prostatic intraepithelial neoplasia to the agent in whole-mounted radical prostatectomy specimens.

A short-term, prospective, double-masked, placebo-controlled, phase II chemoprevention trial with cancer incidence as an end point could be done simultaneously in patients with high-grade prostatic intraepithelial neoplasia without cancer (Fig. 2, B). Chemoprevention trials designed to reverse high-grade cases may be confounded by the presence of underlying but undetected prostate cancer. This difficult problem is addressed by requiring a second biopsy with negative findings for cancer before entry into the study (preferably sextant biopsies with special attention being given to areas of abnormality on ultrasonogram or digital rectal examination) and by including enough subjects in the study and control groups to equalize the risk of coexistent cancer between the two groups (55).

Prostatic intraepithelial neoplasia is routinely monitored by repeat biopsy in contemporary urologic practice. Periodic re-evaluation would be necessary, including physical examination, repeat biopsy, and surrogate intermediate end-point biomarkers. We suspect that sequential prostate needle biopsy specimens will allow good estimation of clinical regression, stabilization, or progression, but they may not identify finer categories of estimation of treatment effect because of sampling error and inability to sequentially repeat the biopsy in the same microscopic focus. If, for example, subjects in a study are treated for 1 year with a chemopreventive agent, prostate needle biopsies at 12 and 24 months will measure different effects and will need to be evaluated separately. If subsequent biopsy reveals prostate cancer, these patients need definitive treatment. Those with prostatic intraepithelial neoplasia or no cancer need continued observation, and it is likely that cancer rates at 5 and 10 years may be the most useful end point for these chemoprevention studies.

This approach, utilizing concurrently performed chemoprevention trials and chemoactive trials, would provide valuable complementary information. Findings would be immediately applicable to long-term treatment for patients with high-grade prostatic intraepithelial neoplasia. These study methods are consistent with current urologic practice and would allow other promising chemopreventive agents to be evaluated in a comparable design. The information gained could provide the basis for additional clinical trials directed toward the prevention and elimination of prostate cancer in other high-risk target populations and in the general population.

**Conclusion**

Prostate cancer is an androgen-dependent malignancy with a long latent period before the appearance of invasive carcinoma. These characteristics and recent advances in our ability to chemically alter the hormonal environment provide an opportunity for early intervention with the intent of decreasing morbidity and mortality from prostate cancer. Chemoprevention trials usually use safely tolerated agents at doses that have minimal, if any, adverse effects. Chemoprevention trials, however, may have different acceptable toxicity tolerance levels according to the agent under investigation and the relative risk of cancer in the study population. Chemoprevention strategies that use high-risk target populations, particularly those with premalignant le-

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**Fig. 2.** A) Proposed protocol for the effects of chemopreventive agents on high-grade prostatic intraepithelial neoplasia (PIN) and cancer before radical prostatectomy. B) Proposed protocol for chemoprevention of prostate cancer in men with PIN. From Bostwick DG, Aquilina JW. Chemoprevention of prostate cancer in men with high-grade prostatic intraepithelial neoplasia [PIN]. NCCTG Insights 1996;3:1-4. By permission of the Journal.
sions, have great potential to shorten the duration of study and require fewer patients, resulting in a significant savings in cost and time. The results from these focused studies, however, should eventually be confirmed in larger scale trials enrolling the general population. Advances in our understanding of the process of carcinogenesis and the availability of promising new chemopreventive agents, including those producing reversible androgen deprivation, have the potential to have a favorable impact on the morbidity and mortality from prostate cancer in the near future.

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