# Chemoprevention Strategies in the Prostate: An Overview

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*Chemoprevention is the administration of agents (drugs, biologics, and nutrients) to prevent induction, inhibit, or delay the progression of cancers. Prostate cancer is an important target for chemoprevention because of its long latency and high prevalence. The development of rational chemopreventive strategies requires knowledge of the mechanisms of prostate carcinogenesis and identification of agents that interfere with these mechanisms. Because of the long time period for prostate carcinogenesis and the large size of the cohort required for an evaluable study, identification and characterization of early intermediate biomarkers and their validation as surrogate endpoints for cancer incidence are essential for chemopreventive agent development. Finally, suitable populations with appropriate risk factors, including the presence of premalignant lesions and genetic predispositions, need to be well characterized for future chemopreventive interventions.* [Rev Urol. *2002;4(2):69–77*]



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The nature and magnitude of the prostate cancer burden has been tracked in the United States and internationally[1] (see http://www.iarc.fr). In the United States alone it is estimated that about 180,000 men will be newly diagnosed with prostate cancer this year, and about 37,000 will die of the disease.[1] In 1998, the National Cancer Institute convened a panel of experts, the Prostate Progress Review Group, to review the progress against this particular cancer and to develop recommendations for strengthening resources and addressing problems and opportunities in this field[2] (see http://osp.nci.nih.gov/prg_access/prg/prg). There is a wish to speed the generation of insights into the biology and behavior of this common tumor and increase the rate of which discoveries are translated into more effective programs of prevention, detection, diagnosis, and treatment (see http://www.nci.nih.gov/prostate).

Prostate cancer presents some unique challenges. Cells that have the appearance of prostate cancer can be found in the prostate gland of nearly half of all men over the age of 50.[3,4] Yet the lifetime risk of a man being diagnosed with a clinically apparent prostate cancer is only 11%, and the lifetime risk of dying of prostate cancer is only 3.6%. Thus three cancers develop for every one that will prove lethal. The ultimate strategy for defeating prostate cancer calls for ways to distinguish these harmless indolent cancers and developing effective ways to prevent or treat the potentially lethal forms of the disease.

Prevention is the ultimate approach to controlling prostate cancer. However, effective prevention will require a thorough understanding of the mechanisms whereby normal prostate tissues become malignant. The use of this fundamental knowledge to develop pharmacologic approaches to arrest or reverse the processes of carcinogenesis is called chemoprevention. Features of prostate cancer, which include prevalence, long latency, screening complexity, and significant mortality and morbidity, provide the need and opportunity for chemoprevention.[5]

New insights concerning the biochemical and molecular pathogenesis of prostate cancer offer great promise for cancer chemoprevention. These new insights have the potential to:

1. Discover new chemopreventive drug targets and drugs relevant to prostate carcinogenesis.
2. Define new endpoint biomarkers as surrogates for prostate cancer development.
3. Identify clinical trial study cohorts at risk for progression of prostate neoplasia that will serve as efficient settings for the evaluation of novel chemopreventive interventions.

## Identifying Promising Chemopreventive Agents in Prostate Cancer

The criteria for selecting chemopreventive agents that are ultimately evaluated in clinical trials can rely on leads from several distinct areas of investigation. Epidemiologic, experimental, and basic mechanistic carcinogenesis data can all provide rationales for pursuing the development of a particular pharmaceutical agent, micronutrient, or dietary substance.[6-8] The safety requirements for a chemopreventive agent may be more stringent than for therapeutic agents in that chronic administration to at-risk normal or asymptomatic individuals may be needed to demonstrate chemopreventive efficacy. For this reason, and because they are not perceived as medicines, food-derived products or dietary micronutrients are highly interesting classes of compounds for evaluation.[9] For example, the epidemiologic data from dietary questionnaires in the Health Professional's Follow-up Study suggested that consumption of tomato products was one of the few discernable food use patterns to be strongly associated with a decreased risk of prostate cancer development.[10] Further studies confirmed that increased serum levels of lycopene, the carotenoid pigment present in large amounts of tomatoes, were more highly correlated to decreased prostate cancer risk than were levels of other circulating, diet-derived carotenoids. From a mechanistic standpoint, it has been shown that lycopene is the most potent antioxidant carotenoid and that the free-radical scavenging activity of these compounds may protect cells against oxidative mutagenesis.[11] The significantly lower levels of serum and tissue lycopene and other natural antioxidants in prostate cancer patients[12] may be indicative of a deficiency state that is either a cause or a consequence of prostate carcinogenesis. Augmentation of serum and intraprostatic lycopene levels by dietary administration in normal and prostate tumor-bearing animals has been achieved,[13,14] and chemopreventive efficacy in several other tumor types has been demonstrated.[15-17]

With further investigation, many promising agents such as lycopene are often demonstrated to have multiple mechanisms of action related to their chemopreventive potential. For instance, recent reports suggest that lycopene in association with α-tocopherol (vitamin E) can inhibit prostate carcinoma cell proliferation at physiologic concentrations in vitro.[18] Other studies have shown that lycopene may interfere directly with IGF-I receptor-mediated growth signaling, an aberrant mitogenic response thought to be in effect in prostate cancer.[19] With all this substantiating information in place, a phase I pharmacokinetic and safety study has been designed to look initially at a food-based lycopene delivery system and then expand the assessment to a defined chemical supplement. Indeed, a preliminary report from a previous study of lycopene supplementation in men with localized prostate cancer showed modulation of prostatic intraepithelial neoplasia (PIN) grade and volume as

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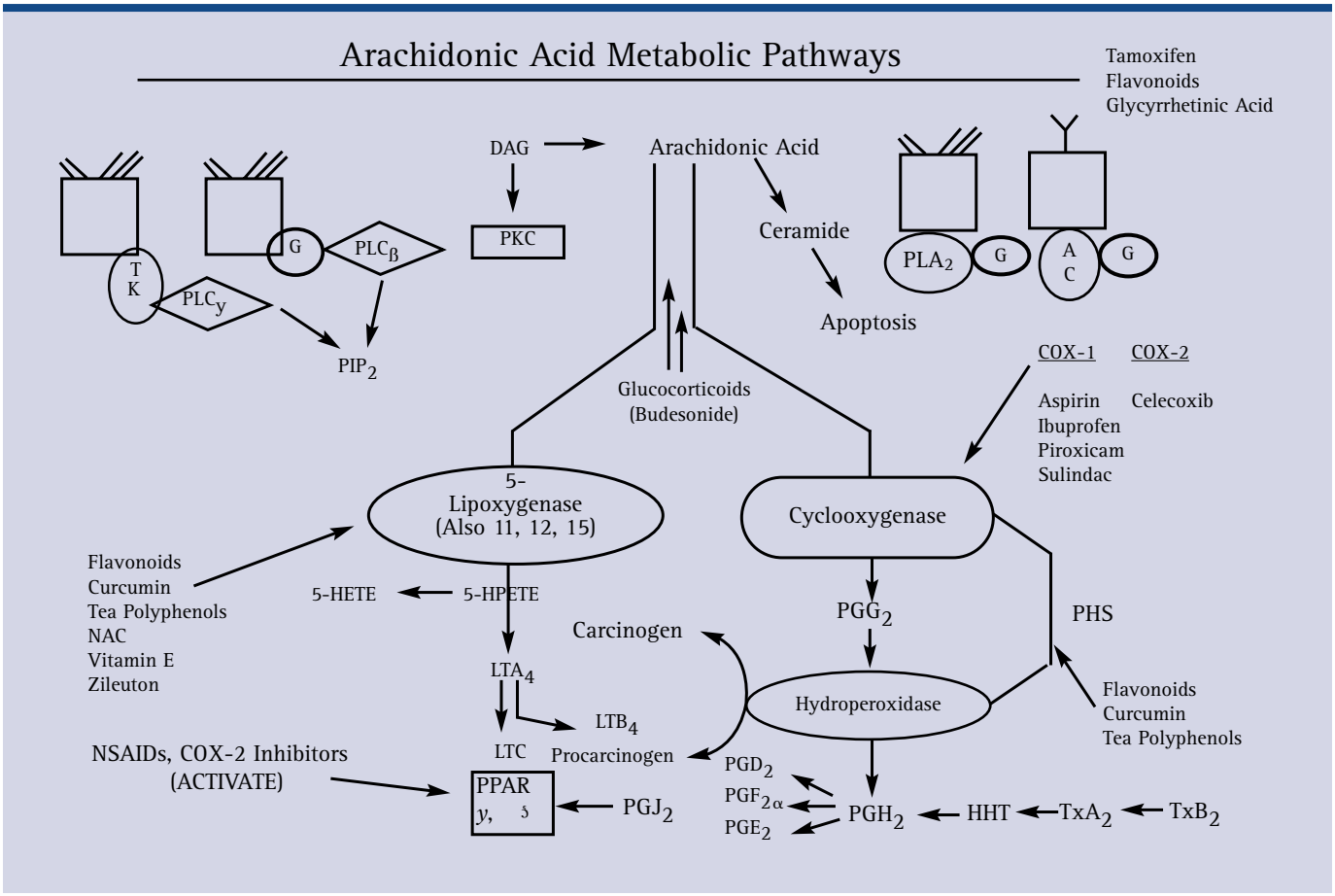
well as decreased serum PSA and proliferation biomarkers after a 3-week intervention prior to surgery.[20]

Even large-scale intervention studies with dietary supplements in other cohorts that failed to show any benefit in the original organ system have provided some of the best leads for prostate cancer prevention strategies. Secondary clinical trial endpoints suggested that selenium (200 µg Se/day) in the form of selenized brewer's yeast was associated with a 63% reduction in prostate cancer in a skin cancer cohort (13 cases in the selenium-treated group versus 35 cases in the placebo group of 974 total men),[21] and a significant reduction in prostate cancer incidence was seen in Finnish smokers taking vitamin E (50 mg/day) compared to controls (32% reduction in 14,564 men receiving α-tocopherol versus 14,569 not receiving it).[22] Both these agents are currently under investigation in cohorts at risk for prostate cancer. Other natural product-based or micronutrient-related substances under investigation as potential prostate chemopreventive agents include soy isoflavones,[23-25] vitamin D analogs, and green tea components.[26,27]

In the past, the toxicity profile of many synthetic pharmaceuticals developed for noncancer indications made them less than optimal for extended administration needed in a chemoprevention protocol. However, today's use of rational drug design methodologies and high throughput screening procedures can produce compounds with precise molecular targets and minimum long-term side effects. A case in point is the new generation of nonsteroidal anti-inflammatory drugs (NSAIDs). Originally developed for the treatment of arthritis and as analgesics, these agents have a very high therapeutic index with markedly reduced gastrointestinal toxicity, the dose-limiting and duration of treatment-limiting characteristic of prototypical NSAIDs such as aspirin or ibuprofen. Systematic investigation of arachidonate metabolic pathways (Figure 1) demonstrated that two distinct isoforms of cyclooxygenase, COX-1 and COX-2, had different roles in the maintenance of gastrointestinal

Figure 1. *Arachidonic acid metabolic pathways.*



(GI) homeostasis and regulation of inflammation. The development of GI-sparing, COX-2 selective inhibitors such as celecoxib has opened the door to the extended use of NSAIDs in a chemoprevention setting.[28] It has long been known that an elevated and aberrant prostaglandin-driven inflammatory response attends many neoplastic processes.[29] Increased expression of COX-2 has been implicated in this process, and epidemiologic and experimental evidence suggests that use of anti-inflammatory agents can control or reverse carcinogenesis.

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Among the tumor types that have been shown to overexpress COX-2 is prostatic adenocarcinoma.[30] Both selective and nonselective COX-2 inhibitors, such as celecoxib and sulindac, respectively, have been shown to be effective in preventing the progression of premalignant colorectal adenomas in preclinical and clinical studies[31-34] as well as in preclinical studies in bladder,[35] skin,[36] and mammary gland.[37] It has been suggested that these NSAIDs may be useful for the prevention or therapy of prostate cancer as well. Indeed, both sulindac and celecoxib have been shown to inhibit the growth or induce apoptosis in human prostate cancer cell lines in vitro,[38,39] and the NSAID flufenamic acid has been shown to inhibit the expression of the androgen receptor in LNCaP cells.[40] Recently, an inverse association between aspirin or ibuprofen use and prostate cancer development was noted in several case control studies.[41,42]

Interestingly, other chemopreventive agents structurally unrelated to synthetic NSAIDs, such as flavonoids, curcumin, and tea polyphenols, also affect arachidonate metabolism, either via cyclooxygenase or the alternative 5-lipoxygenase (5-LO) pathway[43] (see Figure 1), suggesting a pivotal role for prostaglandins and leukotrienes in cancer. For instance, in 122 matched normal and cancerous prostate tissues, 5-LO mRNA expression was elevated in malignant cells.[44] Further support for the involvement of the lipoxygenase metabolic pathway in prostate cancer growth comes from a study showing reduced DNA synthesis and growth inhibition of prostate cancer cells in vitro by specific 5-LO inhibitors.[45] The increased risk of prostate cancer associated with high dietary intake of animal fats shown in multiple population-based studies may in part be explained by the rich sources of fatty acids like arachidonate in these diets that favor conversion to proinflammatory eicosanoids.[46]

A fundamental and universal feature of prostate cancer regulation is hormone dependence,[47] and many ongoing chemoprevention trials are investigating the use of pharmaceutical agents that inhibit testosterone production (eg, finasteride [Proscar]), block the androgen receptor (eg, flutamide, bicalutamide [Casodex]), or short-circuit endocrine signaling (eg, leuprolide). Although acceptable toxicity for these agents in a chemoprevention setting could be somewhat greater than that experienced with the recognized use of finasteride in benign prostatic hyperplasia,[48] it should probably be less than that seen with the antiandrogens in advanced disease.[49] It has been also shown that estrogen derived from testosterone by aromatase action can also play a role in prostate carcinogenesis and that androgen blockade is insufficient to prevent estrogen-driven cell proliferation.[50] Animal models have shown that tamoxifen treatment is effective in suppressing prostate carcinogenesis.[51] Therefore, coadministration of antiestrogens such as toremifene, tamoxifen, or new selective estrogen modulators (SERMs)[52] may be complementary to current androgen modulation clinical chemopreventive study designs.

Other classes of chemopreventive agents (eg, retinoids such as fenretinide [4-HPR][53] and 9-cis-retinoic acid,[54] antiproliferatives such as 2-difluoromethylornithine [DFMO],[55] and apoptosis inducers such as perillyl alcohol) have high potential for preventing prostate cancer. However, the need for new agents with novel mechanisms is urgent. Although proof of principle has often been clearly demonstrated, none of the existing chemopreventive agents is ideal. Particularly promising are strategies involving combinations of agents with synergistic or additive effects. The combination of antiestrogens with antiandrogens was described above, and the combination of an antiandrogen with an antiproliferative (DFMO and bicalutamide) is under evaluation. The complementary chemopreventive mechanisms of action of retinoids, vitamin D analogs, and antiestrogens also suggest that combination treatments with these agents may be worth exploring.[56]

## Criteria for Intermediate Biomarkers Used as Surrogate Endpoints in Prostate Cancer Chemoprevention Studies

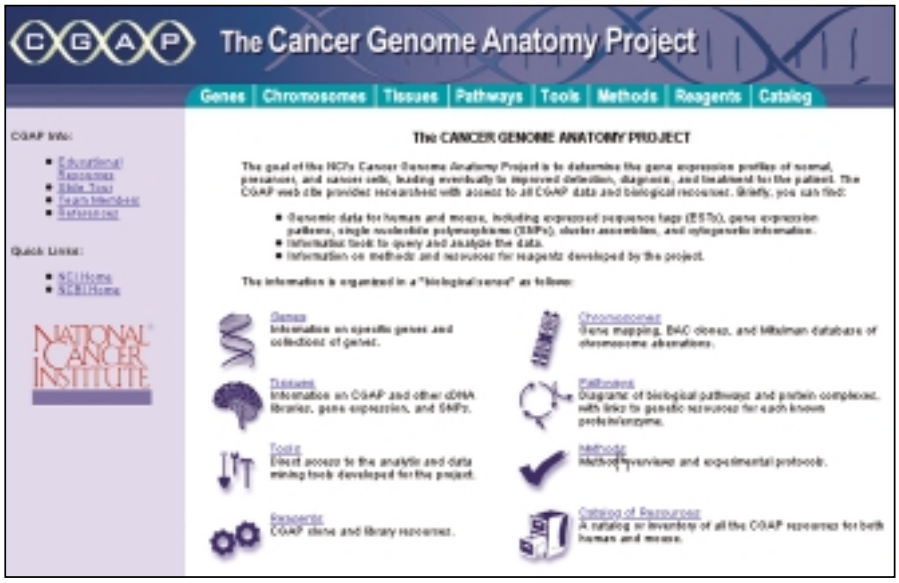
The impracticality of cancer incidence reduction as an endpoint is a major challenge in designing chemoprevention efficacy trials. Therefore, the identification of surrogate endpoint biomarkers (SEBs) is an impor-

tant aspect of the chemopreventive drug development process.[57] The criteria for biomarker relevance are that they must be differentially expressed in normal and high-risk tissue, be closely linked to the causal pathway for cancer, be modulatable by the chemopreventive agent and with a shorter latency than cancer, and, finally, be assayed easily and with quantitative reliability. Prostate-specific antigen (PSA) and the various grades of PIN are considered to be the primary intermediate biomarkers for evaluating efficacy and for identifying appropriate cohorts for chemoprevention studies.[58] Most studies show that most patients with high-grade (HG)PIN will develop carcinoma within ten years.[59] PIN is not usually associated with significantly elevated PSA and is rarely if ever detected by ultrasonography. The only reliable method of detection is biopsy. PIN is associated with abnormalities of phenotype and genotype which are more similar to cancer than to normal prostatic epithelium. Morphologic evidence of an association between the basement membrane-restricted atypia of HGPIN and frank prostate adenocarcinoma includes examples where areas of transition can be identified. Interestingly, a potential early grade PIN-precursor lesion, "proliferative inflammatory atrophy" (PIA),[60] which has recently been described, suggests an etiology of the preneoplasia and a potential rationale for the use of anti-inflammatory agents as chemopreventives. Immunocytochemical evidence of elevated proliferation markers such as Ki-67 and expression of the carcinogen-detoxifying enzyme glutathione-S-transferase in PIA lesions reflects a possible response to electrophile or oxidative stress. In other studies, molecular evidence consistent with PIN progression can be seen from studies using fluorescent in situ hybridization analysis that frequently show increased levels of aneuploidy in individual PIN foci. Similar plus additional chromosome abnormalities in spatially associated cancers suggest a common underlying pathogenesis.[61] Other potential biomarkers are associated with prostate carcinogenesis, including differentiation (eg, blood group antigens, vimentin), apoptosis induction (eg, TUNEL, bcl-2), signal transduction (eg, TGF $\alpha$, c-erb-2, and androgen receptor expression), and biochemical changes (eg, IGF-I levels).

To define better the molecular and cellular alterations associated with prostate cancer progression requires knowledge of specific genes that are differentially expressed in premalignant cells versus cancer, and it is important to understand not only what genes might be involved in susceptibility to carcinogenesis but what gene product targets might be modulated by chemopreventive intervention. To this end, the NCI Cancer Genome Anatomy Project (see http://cgap.nci.nih.gov/) (Figure 2) is seeking to build an index of all genes that are expressed in tumors and is developing technologies that allow Web-based access to these informatics tools. The tumor type with the highest representation in the early versions of the CGAP database is prostate cancer, which should facilitate many research activities in the field, including identification of new SEBs and potential chemopreventive agent molecular targets.

The ultimate proof of chemopreventive efficacy will require correlation of validated morphologic biomarkers to those molecular genetic biomarkers shown to be relevant to cancer progression.[57] For example, since many prostatic lesions progress slowly or not at all, it will be important to ensure that any precancers that are prevented or regressed in a chemopreventive intervention are those that had the potential to progress. Phenotypic chemoprevention could be rigorously demonstrated only with near-complete inhibition of new lesions. With less than this level, it is possible that the remaining lesions were in fact those that would

**Figure 2.** *The NCI's Cancer Genome Anatomy Project website.*



have progressed to cancer. However, by utilizing posttreatment genotypic analysis, if it can be shown that remaining lesions exhibit a decreased incidence of cancer-related changes (ie, either in specific genes or in more general measures of genomic instability) compared to placebo or baseline, a claim for a significant chemopreventive effect could be justified. The "field-effect" carcinogenesis concept suggests that a chemopreventive outcome would be further supported if the genotype of normal-appearing tissue in the target organ was also stable or showed reduced cancer-related change.

Continued research and discussion with the Food and Drug Administration are needed to ensure that surrogate endpoint-based chemoprevention indications are feasible for prostate and other cancers. The best example of the use of surrogate endpoint data to gain marketing approval for a class of agents for disease prevention comes from the lipid-lowering drug/cardiovascular heart disease precedent. Much like carcinogenesis, coronary heart disease (CHD) has a long latency and a surrogate marker, elevated serum cholesterol, that seems to correlate with the pathophysiology of the disorder. Epidemiologic data has long suggested an association between elevated cholesterol and an increased risk of CHD. Clinical trials carried out with the various statins had a basis in the mechanistic rationale of inhibition of cholesterol biosynthesis pathway enzymes. The results of these trials supported approval on the basis of cholesterol-lowering activity and only later did metaanalysis of multiple clinical trials demonstrate conclusively that use of lipid-lowering drugs correlated with an overall reduction in CHD mortality. This model demonstrating long-term clinical benefit in asymptomatic but at-risk individuals should be applied to cancer chemoprevention as well.

### Selection of Cohorts for Prostate Cancer Chemoprevention Trials

Five target populations appear to have the greatest promise for chemoprevention trials in prostate cancer:

1. Patients with HGPIN.
2. Patients with an early cancer scheduled to be treated by watchful waiting.
3. Patients with cancer scheduled for radical prostatectomy 6 to 8 weeks after diagnosis.
4. High-risk patients with elevated PSA values or a family history of early-onset prostate cancer who are biopsied on study entry.
5. Normal men (PSA < 3 ng/mL, normal DRE) from the general population but with some increased risk factors (increased age, racial group, etc).[62]

As shown in Table 1, phase I trials of new potential prostate cancer chemopreventive agents may be conducted in normal volunteers or more advanced cancer patients depending on the degree of confidence and regulatory consensus as to the safety margin of the agent under study. Agents currently under investigation in this category include soy isoflavones and lycopene. Pharmacokinetic assessments, dose-escalation safety determinations, and some surrogate tissue biomarker response data are typically obtained from these trial designs.

Phase II trials to evaluate prostate-specific SEB responses to chemopreventive intervention can be conducted within the context of standard care in several of the cohorts. Phase II studies with flutamide, flutamide/Lupron, flutamide/toremifene, DFMO, DFMO/bicalutamide, soy isoflavones, and a vitamin D analog are ongoing. Testing combinations of chemopreventive agents in these cohorts will be particularly valuable in assessing the safety and potential synergy of agents that function via complementary mechanisms of action.

A phase III study of finasteride, the Prostate Cancer Prevention Trial (PCPT),[63] is now in the sixth year of a projected 10 years duration with more than 18,000 men randomized. At 7 years of treatment, all survivors will undergo sextant biopsy to determine the period of prevalence of prostate cancer. Finasteride was chosen for this study because it reduced the androgenic milieu of the prostate via DHT inhibition, has a relatively low risk of side effects, and inhibits the growth of prostate cells in vitro. Problems associated with this agent are potential biopsy sample bias associated with treatment-associated prostate gland shrinkage and potential PSA detection bias due to inhibition of PSA, which required careful trial design considerations to minimize. However, this agent may not provide chemopreventive benefit in all cohorts. Recently, a smaller study of finasteride in a different cohort (men with elevated PSA but negative pretreatment biopsy) who underwent treatment for a shorter duration (12 months) showed no evidence of chemoprevention and some risk of progression in patients with preexisting PIN.[64] Chemoprevention trials designed to reverse HGPIN may be confounded by the presence of underlying but undetected cancer. This problem might be addressed by requiring a second biopsy without cancer before entry into the study and by including a large-enough sample size to ensure comparable coexistent cancer in both study and control groups.[65]

Another planned phase III study will investigate three year's treatment of patients with HGPIN with selenomethionine (SELECT) with multiple biomarker and efficacy end-

**Table 1**
**NCI, DCP-Sponsered or Funded Phase I/II/III Clinical Chemoprevention Trials: Prostate Cancer**

| Agent | Cohort (Treatment Period) | Endpoint(s) |
|---|---|---|
| **Phase 1** | | |
| Lycopene | Normal volunteers | Pharmacokinetic assessment of single-dose food-based lycopene delivery. Definition of dose range for use in multidose study (3 months). |
| **Phase II** DFMO | | |
| | Scheduled for prostate cancer surgery (4-8 weeks). | Histopathology (PIN grade, nuclear polymorphism, nucleolar polymorphism, ploidy), proliferation biomarkers (PCNA, Ki-67) |
| | Scheduled for prostatectomy (Stage A or B prostatic carcinoma and scheduled for cystoprostatectomy) (14 days) | Drug effect measurements: ODC activity (skin and prostate), polyamine levels (prostate). Histopathology (TRUS-guided biopsies). Biochemical biomarkers: PSA, PAP, testosterone |
| | Serum PSA 3-10 ng/ml (includes patients with prostatic carcinoma and PIN (14 days-1 year) | Drug effect measurements: ODC activity (skin and prostate), polyamine levels (prostate). Histopathology (TRUS-guided biopsies). Biochemical biomarkers: PSA, PAP, testosterone |
| Soy isoflavones | Scheduled for prostate cancer surgery | Histopathology (PIN grade, nuclear polymorphism, nucleolar polymorphism, ploidy). Proliferation biomarkers (PCNA, Ki-67), genetic/regulatory biomarkers (p53, *bcl*-2, pc-1, chromosome 8p loss) |
| Flutamide | Patients with HGPIN (12 months) | PIN grade and incidence, cancer incidence, nuclear polymorphism, nucleolar size, ploidy. Other endpoints: PCNA, angiogenesis, apoptosis, LOH chromosome 8, growth factors, PSA |
| Flutamide/ Leuprolide | Scheduled for radical prostatectomy (12 weeks) | PIN grade and incidence, nuclear polymorphism, nucleolar size, ploidy. Other endpoints: PCNA, angiogenesis, apoptosis, LOH chromosome 8, growth factors, PSA |
| Flutamide/ Finasteride/ Toremifene | Scheduled for radical prostatectomy (4-8) weeks | PIN grade and incidence, nuclear polymorphism, nuclear size, ploidy |
| Fenretinide | Biopsy-proven nonmetastatic prostate adenocarcinoma, scheduled for radical prostatectomy (4 weeks) | Genetic/regulatory biomarkers: TGFß, c-*myc*, p53 plasminogen activators (tPA, uPA), apoptosis |
| Fenretinide | Scheduled for prostate cancer surgery (4-8 weeks). | Histopathology: PIN grade, nuclear polymorphism, nucleolar polymorphism, ploidy. Proliferation biomarkers: PCNA, Ki-67. Differentiation biomarkers: Lewis$^y$ antigen. Genetic/regulatory biomarkers: p53, EGFR, TGF |
| Soy protein | Patients at high risk for biochemical failure postsurgery | Rising PSA, circulating prostate cancer cells (PSM-RT/PCR) |
| Vitamin D analog | Scheduled for radical prostatectomy (4-8 weeks). | Nuclear morphometry, proliferation biomarkers: MIB-1, apoptotic index. Differentiation biomarkers: androgen receptor. Microvessel density: Factor 8 staining, vitamin D receptor and metabolite assay, serum PSA and PSMA levels, plasma TGFß level. |
| NSAID (celecoxib) | Scheduled for radical prostatectomy | Histopathology, proliferation biomarkers: PCNA, Ki-67, p27, p21, apoptotic index DNA adducts. Microvessel density: factor 8 staining, serum PSA levels, prostaglandin assays, COX-1,2 expression. |
| **Phase III** | | |
| Finasteride | Men ≥ 55 years of age with normal DRE and PSA < 3.0 ng/mL) (7 years) | Prostate cancer incidence (grade and stage), BPH incidence and severity, overall and prostate-specific moratility, TURP, PSA levels |
| Selenized Yeast | Skin cancer (melanoma, monmelanoma) patients, low Se areas in US (≈1 year) | PSA levels |
| *l*-Selenomethionine | HGPIN (3 years) | Prostate cancer incidence (grade and stage), PIN grade, other histopathology and proliferation biomarkers |

points evaluated. The clinical design of this trial includes a repeat biopsy (sextant or greater) at an interval after initial HGPIN diagnosis to exclude individuals with coexistent cancer who might confound the findings. All patients will be followed for 10 years from randomization to provide long-term outcomes information.

## Future Directions

Prostate cancer remains an enormous health care challenge, yet technical advances in a variety of areas show promise for the control and treatment of this complex disease. Developments in the areas of molecular risk assessment, diagnostics, and imaging are of particular relevance to the advancement of prevention science. Current efforts to define the genetic susceptibility of individuals to prostate cancer are based on the large variations in familial, racial/ethnic, and geographic differences in incidence and mortality of this disease. Conflicting evidence associating risk with polymorphisms in steroid reductase (SRAD5A2), 17-hydroxylase cytochrome P450 (CYP17), and androgen receptor genes has been reported.[66,67] Linkage analyses in families with multiple cases of prostate cancer have led to the search for a putative hereditary prostate cancer gene (HPC-1).[68] Susceptibility loci on several chromosomes are being explored. Confirmation of results from these studies will eventually provide a means of identifying high-risk cohorts that might benefit from chemopreventive intervention.

Both initial diagnosis of prostate cancer and early assessment of chemopreventive efficacy have traditionally relied on biopsy as the "gold standard" by which other diagnostic methods are judged. Furthermore, biopsy sampling issues can complicate the interpretation of chemopreventive outcomes in certain clinical trial designs. However, advances in imaging science hold the prospect of improving both diagnosis and biomarker analysis. Three-dimensional ultrasonographic image analysis tools developed for brachytherapy will be increasingly valuable in directing the optimal biopsy sampling efforts required for definitive chemoprevention studies. New magnetic resonance imaging technologies[69,70] and enhancing agents[71] may not only improve resolution for staging and biopsy sampling but may point the way to noninvasive molecular spectroscopic evaluation of an individual lesion's risk of progression. ■

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## Main Points

- Chemoprevention involves understanding how normal prostate tissues become malignant and using this knowledge to develop pharmacologic approaches to arrest or reverse carcinogenesis.
- Safety requirements for a chemopreventive agent may be more stringent than for therapeutic agents.
- The free-radical scavenging activity of lycopene may protect cells against oxidative mutagenesis.
- Selenium, soy isoflavones, vitamin D analogs, and green tea components are under investigation as potential prostate chemopreventive agents.
- Epidemiologic and experimental evidence suggests that use of anti-inflammatory agents can control or reverse carcinogenesis.
- Animal models have shown that tamoxifen treatment is effective in suppressing prostate carcinogenesis.
- The complementary chemopreventive mechanisms of action of retinoids, vitamin D analogs, and antiestrogens may lead to effective combination treatments.
- Identification of surrogate endpoint biomarkers is an important aspect of the chemopreventive drug development process.

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