Several approaches in chemoprevention are under investigation to address the increasing incidence of cancers of the bladder and prostate.

**Background:** The incidence of bladder and prostate cancer continues to rise, with little accompanying improvement in management strategies. Opportunities exist for testing various types of chemopreventive interventions.

**Methods:** The authors review the biology of progression to invasive disease for cancers of the bladder and the prostate and identify intermediate disease and surrogate endpoint markers. Candidate interventions and initial clinical trial results are described.

**Results:** Markers of cellular proliferation and differentiation, as well as antigens such as Le\(^x\), M344, DD23, and bladder tumor antigen, are promising for bladder cancer. Testing with prostate-specific antigen and prostate-specific membrane antigen is promising for prostate cancer. Several prevention intervention trials are in progress for both cancers.

**Conclusions:** Vitamins, polyamine synthesis inhibitors, and oltipraz are undergoing clinical tests for chemopreventive effects in bladder cancer, and a large trial of finasteride to prevent prostate cancer is completing accrual. Results from these studies will direct future research.

**Introduction**

Prostate cancer is the most commonly diagnosed noncutaneous cancer in the United States and the second most common cause of cancer death in American men. Since 1990, the incidence of this disease has almost tripled. Many factors contribute to this increase: continuing improvements in the ability to diagnose prostate cancer, the use of prostate-specific antigen (PSA) testing as a screening tool, and an increase in public awareness of the disease due to several prominent individuals having prostate cancer. These factors also may explain the improvement in relative five-year survival over time (Table).

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated Incidence (M)</th>
<th>Five-Year Relative Survival (all ages)</th>
<th>Five-Year Relative Survival (ages 65-74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>334,500</td>
<td>58%</td>
<td>67%</td>
</tr>
<tr>
<td>1996</td>
<td>64,000</td>
<td>54%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Similarly, the incidence of bladder cancer is rising. An estimated 52,900 new cases were expected to be diagnosed in 1996, making it the fifth most common malignancy in Americans. Bladder cancer is expected to cause 11,700 deaths. Unlike prostate cancer, the methods by which bladder cancer is diagnosed (cystoscopy and biopsy) have remained relatively unchanged over the last several decades. Thus, the comparatively high incidence of bladder cancer cannot be attributed to technologic advances.

Increasing age is associated with incidence of bladder and prostate cancers more than with most other malignancies. Between 1990 and 1992, the incidence of prostate cancer in men 40 to 59 years of age was 1 in 78 compared with 1 in 6 for men 60 to 79 years of age. The median ages for bladder carcinoma are 69.0 for men and 71.0 for women. The age-associated incidence of bladder cancer in men increases from 130 to 2,285 per 100,000 for ages 65 to 69 and for ages 85 and older, respectively. The corresponding incidence for women increases from 35 to 65 for ages 65 to 69 and for ages 85 and older, respectively.

By the year 2000, the number of Americans over 65 years of age is predicted to increase by 64%. Thus, within the next few years, prostate and bladder cancers will become greater health concerns. Although several advances have been made in the diagnosis and treatment of prostate and bladder cancer, no effective methods to prevent these malignancies currently exist. However, promising avenues in chemoprevention are now being studied.

**Chemoprevention Strategies**

Primary prevention involves the identification and avoidance of cancer-causing factors. Factors associated with bladder cancer incidence and progression include occupational exposure to chemicals (eg, aniline dyes), cigarette smoking, ingestion of analgesics (phenacetin) or artificial sweeteners, bladder infections, and bladder calculi. Cigarette smoking is the strongest risk factor for developing bladder cancer, but, unlike lung cancer and cardiovascular diseases, the risks are not precipitously...
Secondary prevention involves screening individuals at risk for developing a particular cancer with the goal of early detection and treatment. Screening can help to detect cancer at an earlier stage when more effective treatment can be offered, resulting in decreased mortality. While some evidence supports screening endeavors for bladder cancer and while PSA testing for prostate cancer is widely used, the effect of either on reducing cancer specific mortality has not yet been tested prospectively.

Chemoprevention involves the administration of a natural or man-made agent to retard or prevent the development or progression of cancer. Chemoprevention differs from cancer treatment in that the individuals most appropriate for chemopreventive interventions are generally healthy people at high risk for developing the specific cancer who have not yet contracted the disease. However, most healthy individuals never contract the clinically important disease (even prostate cancer); thus, for practical reasons (eg, achievable sample sizes, durations of follow-up), chemopreventive trials have often focused on individuals with precancerous lesions or with histories of previously treated cancers. Such individuals may already have cancer that has not yet been diagnosed and are actually receiving cancer treatment rather than cancer prevention.

Drugs developed to treat cancer are fundamentally different from those developed to prevent it. Because subjects receiving chemoprevention are both symptom- and disease-free, toxic drugs are not nearly as acceptable in this group compared with cancer patients who are receiving treatment to save or extend their lives. Also, preventive agents are often taken for long periods of time. Similarly, an effective chemopreventive agent will not significantly alter quality of life. An ideal chemopreventive agent is inexpensive, safe and well tolerated with chronic administration, and effective in preventing more than one cancer.

The main goal of administering a chemopreventive drug is to prevent the development of new cancers. Since the long time needed for most cancers, particularly prostate cancer, to develop complicates the evaluation of the effectiveness of chemopreventive agents, intermediate disease biomarkers have thus been recommended as surrogates to assess efficacy.

Intermediate Disease/Surrogate Endpoint Biomarkers

The development of neoplasia is preceded by a complex multistage process involving genetic events that include mutations and deletions. The term "biomarker," when it relates to cancer, usually refers to detectable molecular alterations that reflect different stages in the process of initiation, promotion, and progression of tumors. Valuable biomarkers can include laboratory tests to assess processes that reflect changes often occurring in the epithelium prior to the development of overt cancer. Some can be associated with cellular or molecular events in different stages of carcinogenesis, while others can be an indirect reflection of the quantity of cancer cells present (eg, cytology, PSA).

Cancer prevention trials have proposed biomarkers as endpoints rather than the actual development of cancer (incidence), since the latter requires a long follow-up period and a large number of subjects. With surrogate biomarkers, many drugs can be investigated with fewer subjects for shorter periods of time. Other potential uses of biomarkers include early detection, monitoring of disease progression, risk assessment, and prognostication of disease outcome and therapeutic response.

In general, markers of early bladder lesions can be classified as pathologic, genetic, or biochemical. Pathologic markers include cellular proliferation and differentiation that can be detected histologically or cytologically, such as standard cytology, immunohistochemical stains for proliferating cell nuclear antigen (PCNA) or Ki67, mitotic indices, etc. Genetic markers include changes in DNA ploidy status (by flow cytometry or image analysis), chromosomal aberrations detected by cytogenetic or molecular analyses, and DNA microsatellite repeat alterations. Quantification of apoptosis (programmed cell death) also can be used as an endpoint in chemopreventive studies. Promising biochemical markers useful in bladder cancer chemopreventive studies include the Lewis blood-group antigen (Le) and other tumor-associated antigens such as M344, DD23, and the "bladder tumor antigen." A number of markers used in prostate cancer prevention studies include biochemical markers (PSA and prostate-specific membrane antigen), proliferation markers (increased S-phase fraction), genetic markers (DNA ploidy status), and histologic markers (prostatic intraepithelial neoplasia and angiogenesis).

PSA is the most important and clinically useful marker for prostate cancer. It is a 34-kD serine protease whose expression is primarily but not exclusively restricted to prostatic epithelial cells. It catalyzes the liquefaction of the seminal coagulum after ejaculation. Elevated PSA levels are seen in both benign and pathologic processes, including prostatitis, benign prostatic hyperplasia, and adenocarcinoma of the prostate. The prostate enlarges with advancing age and more PSA is produced, and it also is elevated transiently following prostate biopsy or trauma. PSA gains access to the bloodstream with any process that causes stromal or acinar basement membrane disruption. The majority of measured PSA in serum is complexed with alpha-1 antichymotrypsin. Free (uncomplexed) PSA is found in a much lower concentration than complexed PSA in serum. Patients with prostate cancer have a higher percentage of their total PSA in complexes. Whether the ratio of free PSA to total PSA is more useful than total PSA alone is still under investigation.

Oesterling et al advocate the use of age-specific PSA to make the test more sensitive in younger men and more specific in older men. More recently, Morgan et al showed that if the current normal PSA ranges of 0 to 4 ng/mL are used, 40% of prostate cancer cases would be missed in black men based on age-specific ranges that were developed based on data from white men. Black men with newly diagnosed prostate cancer were found to have higher PSA levels than white men, even after corrections were made for age, tumor grade, and tumor stage. To detect the disease in black men, who have a higher prostate cancer mortality than any other racial or ethnic group, Morgan et al propose the use of race-specific PSA levels. For the last several years, PSA has been increasingly used not only in detecting prostate cancer, but also in monitoring patients with prostate cancer and their response to therapies.

The c-erbB-2 oncogene codes for a transmembrane growth factor receptor that is 43% homologous to the epidermal growth factor receptor, which has been previously described as a biomarker. It is thought to be involved in cell growth and differentiation. Expression of c-erbB-2 is a strong indicator of prostate cancer progression. Inactivation of p53, a tumor suppressor gene on chromosome 17p, is seen in up to 25% of advanced primary prostate cancer and in up to 50% of metastases. Likewise, the loss of expression of the retinoblastoma gene on chromosome 13q is seen in a minority of advanced prostate cancer, thus suggesting its possible use as a biomarker. These molecular markers (epidermal growth factor receptor, c-erbB-2, p53, and retinoblastoma) also have been associated with other malignancies including bladder cancer, thus supporting the possibility that a preventive agent that could reverse these molecular events (or suppress their consequences) for one tumor site may be effective in preventing a variety of tumors. The development and validation of biomarkers to be used as surrogate endpoints for developing cancer are important to the success of testing chemopreventive agents.
blind trials in which the chemopreventive agent is given vs a placebo (or two preventive regimens are tested against each other) with the goal of reducing the incidence of diagnosis of the specific cancer being tested.

**Chemoprevention of Bladder Cancer**

Bladder cancer is appropriate for chemoprevention trials for four reasons. (1) It is a recurring disease in which the risk of recurrence and progression increases with large and multiple tumors as well as with vascular, lymphatic, and basement membrane involvement. (2) Bladder cancer usually presents as superficial tumors that are easily resected transurethrally. (3) The bladder can be evaluated noninvasively (cytology, DNA flow cytometry) for early or premalignant lesions. (4) Normal monitoring of patients with superficial tumors involves surveillance cystoscopy and bladder wash cytology with a low threshold for obtaining biopsies. While patients at risk for recurrence who are currently tumor-free take part in chemoprevention studies, some actually may be receiving treatment as opposed to prevention. Perhaps the best way to ensure that these are truly prevention studies is to perform cystoscopy on these subjects at three to six months following tumor resection and enroll them only if they are determined to be tumor-free. Eventually, if agents are well tolerated and proven to prevent recurrences in patients with prior bladder tumors, they will be tested in subjects who are at risk for developing bladder cancer but have never had a tumor. Approaches that have been used in chemoprevention of bladder cancer include the use of vitamins, polyamine synthesis inhibitors, and dietary factors.

**Vitamins**

While 13-cis-retinoic acid, the vitamin A analog, is effective in preventing bladder tumor growth, it also is associated with multiple side effects (eg, conjunctivitis, pruritus, and joint or eye pain). Using flow cytometry and DNA cytology as intermediate endpoints, Decensi et al showed that N-(4-hydroxyphenyl)retinamide (4-HPR) caused reversion to normal cytology examinations in patients with previously suspicious or positive findings. In contrast, beta-carotene and vitamin E were tested in 50- to 59-year-old healthy Finnish male smokers, and no influence on bladder cancer development was noted. These compliant patients were followed for five to seven years. It is possible that the processes of carcinogenesis were so significant in this high-risk group of patients that even the best chemopreventive agents could have failed. Likewise, no decrease in recurrence was observed in patients with superficial tumors who were given vitamin B6 (pyridoxine).

In a study of 65 patients in 1994, Lamm and associates reported high-dose multivitamins (40,000 U of vitamin A; 100 mg of vitamin B6; 2,000 mg of vitamin C; 400 U of vitamin E; and 90 mg of zinc) resulted in a decreased recurrence rate compared with minimum daily requirement (MDR) doses of these vitamins in a high-risk group of patients with superficial bladder cancer. The patients also received intravesical bacillus Calmette-Guérin (BCG) with and without percutaneous BCG. This study is limited due to its small size and because the administration of BCG could be a confounding variable. Also, the MDR-vitamin-plus-BCG arm did poorly compared with other studies in which BCG alone was given. A larger study assessing the efficacy of megavitamins is being considered.

**Polyamine Synthesis Inhibitors**

The polyamines are normal cell constituents that are thought to be involved in the regulation of proliferation and differentiation and are critical for the process of tumor promotion. Ornithine decarboxylase (ODC) is the rate-limiting enzyme in polyamine synthesis and appears to be involved in the process of tumor promotion. difluoromethylornithine (DFMO) is an irreversible inhibitor of this enzyme. The chemopreventive ability of DFMO ability has been studied in several animal models. A phase I trial previously conducted in human beings revealed dose-limiting toxicities, which usually have been thrombocytopenia and ototoxicity, particularly in patients previously treated with chemotherapy. However, Loprinzi et al recently showed that doses of 0.125 to 1.0 g/d can be given without untoward effects when administered for periods of up to 12 months to middle-aged and elderly individuals.

**Oltipraz**

Oltipraz (5-[2-pyrazinyl]-4-methyl-1,2,3-thione) is currently undergoing phase I trials in the United States. Originally developed as an antischistosomal agent, it was found to protect against chemically induced carcinogens in the lung, stomach, colon, and urinary bladder in animals. The mechanisms of oltipraz action include enhancement of DNA repair processes, induction of phase I enzymes (cytochrome P450) that enhance carcinogen detoxification, and nucleophilic trapping of reactive intermediates, among others. Oltipraz inhibits carcinogenesis induced by polycyclic aromatic hydrocarbons and N-nitrosamines - agents that constitute some of the carcinogenic components of tobacco. Since bladder cancer is more than twice as common in smokers as in nonsmokers, oltipraz may be useful in preventing the development of cancer in smokers. Phase I trials conducted in the United States have shown that the maximum tolerated dose is approximately 125 mg/d for up to a six-month period. Dose-limiting toxicities include photosensitivity, heat intolerance, gastrointestinal toxicities, and neurologic toxicities. Ongoing studies are monitoring optimal dosing and pharmacodynamic action. Oltipraz is unique in its dual capacity as an antischistosomal and anticarcinogenic agent. Its chemopreventive abilities can be effective in patients with histories of Schistosoma haematobium bladder infections, who are at increased risk for developing bladder cancer.

**Urinary pH**

The use of agents or dietary factors to alter the urinary pH also has potential as bladder cancer preventives. Sidransky et al reported that rats with acidic urine did not develop saccharine-induced bladder cancer. In a study comparing individuals with bladder cancer to those with benign prostatic hyperplasia, patients with bladder cancer had higher urine pH concentrations. The antitumor activity of some of the agents discussed previously may well be secondary to their urine pH lowering effect.

**Chemoprevention of Prostate Cancer**

The long latency period and generally slow progression of prostate cancer make it an excellent potential selection for chemoprevention approaches. Unlike bladder cancer, however, direct inspection of epithelium and access to tissue are not as easy. Also, intermediate disease markers (except PSA and prostatic intraepithelial neoplasia) are less well described as they are for bladder cancer. Several chemopreventive agents have been studied both in humans and in animal carcinogenesis models of prostate cancer. These include finasteride, DFMO, and the retinoids.

**Finasteride**

Testosterone and its active metabolite within the prostate, dihydrotestosterone (DHT), are necessary for prostatic epithelial growth. Several treatment agents for prostate cancer interfere with this process at different levels. Finasteride inhibits 5-alpha reductase, the enzyme that catalyzes the formation of DHT from testosterone. This drug is used in the treatment of benign prostatic hyperplasia. Its side effects include decreased sex drive, decreased ability to achieve an erection, and decreased ejaculatory volume. However, these side effects (except for the last) occur in a minority of patients, and they are reversed with discontinuation of the drug. The progression of hormone-sensitive prostate cancer stops with androgen deprivation or estrogen treatment. This forms the basis for the use of finasteride as a chemopreventive agent.
The Prostate Cancer Prevention Trial, which began in the fall of 1993, compares finasteride to a placebo with the endpoint being biopsy-proven presence or absence of prostate cancer. A total of 18,000 men aged 55 years and older have enrolled. They are healthy individuals with normal digital rectal examinations and no significant urinary symptoms. Half of the men receive 5 mg of finasteride daily, and the other half receive placebo for seven years. All will undergo prostate biopsy at the completion of the study to detect the presence or absence of cancer. More than 200 locations across the country are involved in this trial. While prostate cancer prevalence and mortality are highest among black men, only a 4% black participation has been noted. Also, the proportion of Hispanic participation is only 2.5%. To ensure that the study findings are applicable to minority groups, efforts are being made to enroll these ethnic populations to reflect their proportion in the US population. The results of this study will be available in 2003.

*DFMO*

The mechanism of action of DFMO has been discussed previously. The prostate contains high concentrations of polyamines and polyamine synthesizing enzymes, including ornithine decarboxylase (ODC). ODC in the prostate is more susceptible to DFMO inhibition than in other organs. Human and rat prostates are similar in their polyamine content. The administration of DFMO in adult rats caused a reduction of more than 50% in prostate weight while the weights of other organs decreased slightly. DFMO has chemopreventive activity in rat mammary glands, rat skin and bladder tumors, and the mouse colon. Several studies are underway to determine if DFMO has the same preventive effects in human beings. DFMO taken for two weeks at a well-tolerated daily dose (0.5 g/m2) reduces concentrations of prostatic tissue putrescine (the polyamine that is the direct product of ODC action) and thus has biochemical efficacy in prostatic tissue (Messing et al, unpublished data, 1997). It is not known if longer periods of administration will have clinically important prostate cancer preventative properties.

*Retinoids*

Not all of the biologic mechanisms of action of the retinoids are known. Among other things, they inhibit growth by suppressing neovascularization or angiogenesis. Many clinical trials using retinoids (eg, retinoids, 13-cis-retinoic acid, fenretinide) are ongoing. They will test the ability of the retinoids to prevent tumors in several organs including bladder, prostate, lung, breast, head and neck, and skin. Hong et al demonstrated that high doses of 13-cis-retinoic acid (50 to 100 mg/m2 per day for one year) decreased the incidence of second primary tumors in patients with squamous cell carcinoma of the head and neck. These clinical trials will be useful in assessing the efficacy and safety of the retinoids as chemopreventive agents in humans.

*Dietary Factors*

Epidemiologic studies show that dietary factors inhibit carcinogenesis in humans. A high-fat diet may increase the risk of prostate cancer. Compared with American men, Japanese men have a lower incidence of latent prostate cancer, and a lower likelihood of developing clinically significant prostate cancer. Moving to the United States, however, raises their risk, which has been attributed to the increased fat in American diets compared with Japanese diets.

**Conclusions**

The clinical challenges associated with cancers of the prostate and bladder will increase as our population ages. Despite advances in drug development and screening, more people are succumbing to these malignancies. Chemopreventive agents hold promise in this battle. Future chemoprevention trials will include multiple agents in combination with dietary alterations. The combination of agents will allow interventions at different steps in the carcinogenic process. The recurring nature of bladder cancer and the generally slow progression of prostate cancer make these malignancies suitable targets for chemopreventive efforts.

**References**


From the Department of Urology, University of Rochester Medical Center, Rochester, NY.

Address reprint requests to Dr Messing at the Department of Urology, Box 656, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642.