



Review

Prostate cancer chemoprevention: Current status and future prospects

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Abstract

Chemoprevention is a strategy that aims to reduce the incidence and burden of cancer through the development of agents to prevent, reverse or delay the carcinogenic process. Prostate cancer is a suitable target for prevention because it has a high incidence and prevalence, as well as a long latency and disease-related mortality, and furthermore it is a disease in which lifestyle and environmental factors may play critical roles. The development of chemoprevention strategies against prostate cancer will have a huge impact, both medically and economically. Large-scale clinical trials suggest that some agents such as selenium, lycopene, soy, green tea, vitamins D and E, anti-inflammatory and inhibitors of 5 α -reductase are effective in preventing prostate cancer. Although each agent has the potential to affect the natural history of the disease, it is important to develop strategies to strategically proceed for the design and selection of test agents in order to demonstrate clinical benefit with the minimum of adverse effects. Appropriate selection of agent(s), disease stage, trial design and endpoints is critical in selecting the most promising regimens to accomplish these goals. This review highlights the present status of prostate cancer chemoprevention and discusses future prospects for chemopreventive strategies that are safe and clinically beneficial.

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Introduction

In recent years, cancer chemoprevention emerged as one of the major approaches for reducing cancer burden. The term ‘chemoprevention’ was first introduced by Michael B Sporn in 1976, referring to the prevention of cancer development by natural forms of vitamin A. This strategy seems to be promising for reducing cancer incidence both in well defined “high-risk” groups and also in the general population with “low-risk” of developing cancer. Chemoprevention, by definition, is a strategy for pharmacological intervention with naturally occurring and/or synthetic compounds that may prevent, inhibit or reverse carcinogenesis or suppress the development of invasive cancer (Sporn and Suh, 2002). The expanded definition of cancer chemoprevention is to inhibit or delay the development of neoplasia by blocking neoplastic inception as well as reversing the progression of transformed cells before the appearance of malignant lesions (Shukla and Gupta, 2005). In recent years, cancer chemoprevention has matured substantially and has been increasingly recognized by National Cancer Institute (NCI) prevention branch, American Society of Clinical Oncology (ASCO), American Cancer Society (ACS), American Association for Cancer Research (AACR) and some private foundations such as American Institute for Cancer Research (AICR) and Cancer Research and Prevention Foundation (CRPF). The development of chemopreventive agents is the major objective of the Chemoprevention Branch of the Division of Cancer Prevention (DCP) at NCI. The NCI-DCP aims to develop and implement research through clinical trials, screening and testing of new agents and identification of surrogate endpoint markers or cancer incidence reduction. The NCI also supports small- and large-scale clinical trials for this purpose. The overall goals of these programs are to achieve reduction in cancer incidence and mortality as well as to improve the quality of life in high- and low-risk individuals.

Cancer chemoprevention

Successful implementation of chemoprevention depends on a mechanistic understanding of carcinogenesis at the molecular, cellular and tissue levels. Carcinogenesis is a multi-step, multi-path and multi-focal process which involves a series of epigenetic and genetic alterations that begin with genomic instability and end with the development of cancer. At the molecular level, this process involves activation of oncogenes, loss of function of tumor suppressor genes, modulation in genes related to growth regulation, cell cycle, apoptosis, metastases, angiogenesis, as well as alterations of modifier genes (genes involving carcinogen metabolism, methylation, DNA repair and genomic stability) (Shukla et al., 2004). At the cellular and

tissue levels, successive genetic and molecular alterations lead to a gradual transition, usually occurring over several years or even decades, from normal to increasing grades of dysplasia, and finally resulting in an invasive and metastatic phenotype. This long and complex process presents opportunities for the development of clinical interventions both in preventing cancer initiation and in treating the neoplasm during its premalignant stages. The most preferred chemoprevention strategy lies in intervention at the early stage of carcinogenesis *viz.* at the stage of intraepithelial neoplasia (IEN) using natural or synthetic agents with the ability to delay, arrest or even reverse the carcinogenic process.

The most rational approach to cancer chemoprevention is to design and test new agents that act on specific molecular and cellular targets (Lippman and Hong, 2002). There are at least two strategies for the development of chemopreventive protocols. One is to identify natural dietary agents through epidemiological studies demonstrating the effect of agent(s) in cancer incidence and mortality, geographic variations and migration associated changes in dietary and lifestyle practices. A second approach relies on designing and synthesizing of molecular target-based agents. These approaches require isolation, characterization and preclinical evaluation of test agents for their development as chemopreventive agent. This strategy is a large undertaking that will require the coordinated research efforts of pharmaceutical and biotechnology companies, as well as those of the government. The NCI-DCP has initiated the RAPID program which provides a foundation for the development of potential chemopreventive agents by making the resources of DCP available to academic investigators (Crowell, 2005). The RAPID program encourages and supports compound synthesis and formulation under Good Manufacturing Practices regulations, preclinical efficacy and toxicity testing and regulatory support through phase I clinical testing. The details of the RAPID program can be viewed at <http://www.cancer.gov/prevention/rapid/index.html>. Agents that are under development within the RAPID program are shown in Table 1. The criteria for an ideal chemopreventive agent are (i) significant reduction in cancer development, (ii) minimal side-effects, (iii) ease of administration, (iv) known mechanism of action and (v) cost effective as prolonged administration is likely. Currently, more than 40 compounds are being studied in cancer chemoprevention trials in the United States, either as single agents or in combination; details of these studies can be viewed at the NCI website (http://www.cancer.gov/clinical_trials/). These agents have been shown to have varying levels of clinical efficacy in the three categories into which prevention may be typically divided: (i) *primary*, where the goal is to prevent the onset of the disease, selecting healthy cohorts that are at “high-risk” for disease, (ii) *secondary*, aimed at treating a population with an established

Table 1
Agents under development in the NCI RAPID program

Agent	Investigator	Institute
Synthetic triterpenoid	Michael B Sporn	Dartmouth Medical School
Porphyrin polyamine conjugate	Russell F Jacoby	University of Wisconsin-Madison
Synthetic vitamin E derivative	Kimberley Kline and Bob G Sanders	University of Texas at Austin
Sulforaphane derivative	Paul Talalay	Johns Hopkins University
Synthetic indole-3-carbinol derivative	Ling Jong	SRI International
Dietary polyethylene glycol (PEG)	Denis E Corpet	
Mushroom extract (1SY16)	Insu P Lee	Kanazawa University, Japan
Myochemicals in shiitake mushrooms	Thomas M Badger	University of Arkansas
Topical Niacin prodrug	Elaine L Jacobson	University of Arizona
Flavonoid tricin	Andrew J Gescher	University of Leicester, UK
HPV-like particle vaccine	Robert C Rose	University of Rochester
9- <i>cis</i> -UAB30 (RXR)	Donald D Muccio	University of Alabama
Antioxidant from turmeric (<i>Curcuma longa</i>)	Leela Srinivas	Adichunchannagiri Biotechnology, India
Synthetic vitamin D analog	Thomas W Kensler	Johns Hopkins University
Human papillomavirus vaccine	Robert L Garcea	University of Colorado
Flavonoids	John M Pezzuto	Purdue University
Isothiocyanate: sulforaphane	Fung-Lung Chung	Georgetown University
Triterpenoids	Michael B Sporn	Dartmouth Medical School
Marine-derived products	Peter Collin	Coastside Research
Selenium containing amino acid	Clement Ip	Roswell Park Cancer Institute
Fluasterone	Arthur G Schwartz	Temple University
5,6-dihydro-4 <i>H</i> -cyclopenta-1,2 dithiole-3-thione	Thomas W Kensler	Johns Hopkins University
4'-Bromoflavone	John M Pezzuto	Purdue University
Farnesol and Geraniol	Harold L Newmark	Rutgers, State University of New Jersey
Developmental peptides	Eytan R Barnes	The Society of the Investigation of Early Pregnancy

Source: <http://www.cancer.gov/prevention/rapid/projects.html>.

pre-malignant condition or an *in situ* neoplasia, thereby blocking its evolution to cancer, and (iii) *tertiary*, with the intent to prevent the onset of second primary tumors in subjects previously cured of cancer.

Before proceeding to clinical trials, it is essential that the efficacy and safety of chemopreventive agents are validated in experimental models. The development process for establishing a particular test agent is basically similar to the process of evaluating an investigative new drug (IND) for approval by the US FDA. It starts with preclinical evaluation both in cell culture systems and relevant preclinical models and then continues stepwise to clinical trials. The design of clinical chemoprevention trials continues to evolve, but a few generalities about each phase can be defined. In phase I studies, the dose-related safety of drugs is determined; this research includes pharmacokinetic investigations. Initial doses and schedules should be based on toxicity and efficacy data from preclinical models. In phase II trials, a randomized, masked, placebo-controlled design is used to evaluate dose–response and common toxic effects which may be likely to result from long-term administration (usually 3 months or longer). Dose-escalation studies are performed in these trials, which should incorporate measurement of previously validated surrogate biomarkers. Phase II trials can be performed in individuals with pre-malignant lesions or patients cured of an initial cancer but at risk of developing a second primary tumor. If safety and efficacy are judged to be satisfactory in these trials, evaluation of the agent proceeds to randomized, prospective, large-scale phase III clinical trials. These are the ultimate tests of drug efficacy, measuring the incidence of primary tumors as well as surrogate biomarkers, in

relation to dose and toxicity. The longer times involved necessitate assurances of reproducibility of the formulation and long-term drug compliance.

Prostate cancer chemoprevention—clinical trials

Prostate cancer represents in many ways an ideal candidate for chemoprevention because of its high incidence and long latency period before the development of clinically evident disease (Klein, 2005). A large group of men who have a negative biopsy for prostate cancer but have rising PSA levels are advised for ‘watchful waiting’ and are turning to clinicians to find out steps to reduce the risk of being affected by the disease. Appropriate evidence-based studies are needed to test the efficacy of various chemopreventive agents at various stages of prostate cancer. Growing evidence supports the efficacy of cancer chemoprevention and several agents including selenium, vitamin D and E, green tea, lycopene, soy isoflavones, anti-inflammatory and agents targeting androgen and estrogen receptor signaling are being evaluated in various prostate cancer prevention trials. Currently, several NCI sponsored prostate cancer clinical trials are in progress at various institutions in the United States (Table 2).

Prostate cancer chemopreventive agents in phase III clinical trials

Vitamin E and selenium

These agents gained recognition after large randomized clinical trials suggested their usefulness in reducing the risk of

Table 2
Prostate cancer clinical trial ongoing in the United States

Agent	Institute
Exisulind	Mayo Clinic
Celecoxib	Johns Hopkins
Soy isoflavones (genistein)	Wayne State University
L-Selenomethionine	Roswell Park Cancer Institute/SWOG
Selenium yeast	University of Arizona
Di fluoromethyl ornithine (DFMO)	University of California-Irvine
Toremifene	University of Pittsburgh
DFMO and bicalutamide	University of Alabama
Vitamin D analog (Hectorol)	University of Wisconsin
Vitamin E, C and multivitamin	Brigham and Women's Hospital
Soy isoflavones (genistein)	Northwestern University
Selenium	Southwest Oncology Group
Calcitriol	Robert Wood Johnson Medical School
Fish oil	Oregon Health and Science University
Aspirin	University of Washington
Lycopene	University of Illinois

Source: <http://www.cancer.gov/prevention/pucrg/prostatetrials.html>.

prostate cancer. In the Alpha Tocopherol Beta Carotene (ATBC) cancer prevention study in which 29,133 male smokers were randomized into groups ingesting either α -tocopherol (50 mg/day) and/or β -carotene (20 mg/day) in an attempt to assess efficacy in preventing lung cancer, the incidence of prostate cancer was reduced by 32% in men receiving α -tocopherol compared to control group, which did not receive it (Clark et al., 1998). More recent studies have shown that α -tocopherol ingestion correlates with a lower risk of developing prostate cancer. This effect has been attributed to two major vitamin E fractions: α - and γ -tocopherol (Weinstein et al., 2005). Although doses of vitamin E in the range of 400 IU/day are often recommended by clinicians, recently published evidence suggests that the recommended dose should be ≤ 150 IU/day. In a recently reported meta-analysis of 19 trials, recruiting 135,967 participants, 9 of 11 trials testing high-dosage (<400 IU) vitamin E showed a greater risk for all-cause mortality for those on vitamin E than in controls. The difference in mortality risk in high-dosage vitamin E trials was 39 per 10,000 persons (95 CI, 3–74; $P=0.035$). For low-dosage vitamin E trials, the risk difference was -16 per 10,000 persons (CI -41 to -10 ; $P>0.2$). A dose–response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk for dosages of >150 IU/day (Miller et al., 2005).

Selenium is a trace nutrient essential for the activity of glutathione peroxidase, which may reduce oxidative damage to DNA. Several studies have suggested its usefulness in chemoprevention of prostate cancer, but the best (and still indirect) evidence comes from a randomized trial on selenium supplementation from the National Prevention of Cancer Study of 974 men who were given a 200- μ g/day dose of selenium in 0.5 g high-selenium yeast; the study demonstrated 63% reduction in the incidence of prostate cancer (Meuillet et al., 2004 and references therein).

The magnitude of the changes in prostate cancer incidence observed in the trials described above prompted large-scale prospective studies of prostate cancer chemoprevention. The

Selenium and Vitamin E Cancer Prevention Trial (SELECT) sponsored by the NCI is a randomized, prospective, double-blind study designed to determine whether a 7- to 12-year regimen of daily selenium, vitamin E supplements, or both, or placebo in a 4-arm intervention design will decrease the risk of prostate cancer in healthy men. Study supplements include 200 g L-selenomethionine, 400 IU/day racemic α -tocopherol and an optional multivitamin that does not contain either selenium or vitamin E. Each SELECT participant undergoes routine clinical evaluations, including a yearly DRE and PSA test. The target accrual is 32,400 individuals, and the results are expected to be announced in 2013. The true safety and effectiveness of selenium and vitamin E should become clearer when the results of the SELECT study become available (SELECT details available at <http://www.crab.org/select/>).

5 α -reductase inhibitors

In 1993, another prostate cancer prevention trial (PCPT) was initiated and funded by NCI to investigate chemoprevention of prostate cancer with the 5 α -reductase inhibitor finasteride. In this study, 18,882 men participated who had normal DRE and a PSA level of <3.0 ng/ml and were randomized to either finasteride 5 mg/day or placebo for 7 years. Prostate biopsy was advised if the PSA rose to >4.0 ng/ml or the DRE became abnormal. Prostate cancer was detected in 18.4% of men in the finasteride group and 24.4% in the placebo group. The finasteride reduced the period of prevalence of prostate cancer by 24.8% ($P<0.001$), compared with placebo. However, tumors were of Gleason score 7–10 in 6.4% of the finasteride-treated men, compared with 5.1% of the placebo group ($P=0.005$), and sexual side-effects were more common in the finasteride arm. The PCPT was stopped prematurely in 2003 following the recommendation of the Data Safety and Monitoring Board after it was established that the primary endpoint has been met (Thompson et al., 2006). The explanation for more aggressive tumors in the men treated with finasteride so far remains elusive. The PCPT details are available at <http://www.cancer.gov/pcpt>.

Another phase III clinical trial using 5 α -reductase inhibitor is the Reduction of Prostate Cancer Events trial (REDUCE) which will evaluate dutasteride, a dual inhibitor of both 5 α -reductase types 1 and 2 (Andriole et al., 2004). Dutasteride suppresses levels of dihydrotestosterone by $>90\%$, compared with a suppression of $\sim 70\%$ with finasteride. So far, 8000 men have been recruited to receive either 0.5 mg of dutasteride or placebo for 4 years. The results of this study will not be available for some time yet, but may shed new light on the subject of the effectiveness of dutasteride in preventing prostate cancer.

Prostate cancer chemopreventive agents in phase I and II clinical trials

Selective COX-2 inhibitors

Inhibition of COX-2 expression blocks its pro-inflammatory effects, reduces expression of androgen receptors and androgen-inducible genes and promotes apoptosis in prostate cancer cells. Selective COX-2 expression has been observed in high-grade

PIN, a putative precursor of prostate cancer, suggesting a role early in carcinogenesis (Hussain et al., 2003). These results support the hypothesis that inhibition of COX-2 may be an effective preventive strategy for prostate cancers; however, an industry-sponsored large-scale trial of rofecoxib was closed after the drug was withdrawn from the market because of concerns over its cardiovascular safety. In another study, the biological activity of celecoxib was assessed in men with recurrent prostate cancer who had undergone radical prostatectomy and/or radiation therapy, following PSA doubling times (DT) as outcome variables (Smith et al., 2006). This study was also terminated early due to concerns about possible cardiovascular side-effects. Before discontinuation, 78 men were randomly assigned to either celecoxib (400 mg/twice daily) or the placebo group. Eight (20%) of 40 men in the placebo group and 15 (40%) of 38 men in the celecoxib group had post-treatment PSADT of more than 200% of baseline PSA doubling time with no new metastases ($P=0.08$). Mean PSA velocity increased by 3.0% for the placebo group and decreased by 3.4% for the celecoxib group ($P=0.02$). Although the primary efficacy objective was not met, this study provides some evidence for biologic efficacy of celecoxib in treating prostate cancer. Compared with placebo, celecoxib significantly decreased mean PSA velocity and tended to increase the proportion of men who doubled their PSADT.

Selective estrogen receptor modulators (SERMs)

Interest in SERMs as preventive agents has been stimulated by an apparent role of estrogens in the pathogenesis of prostate cancer, through promotion of cell growth. SERMs are generally considered to be ‘weak estrogens’ because they possess both agonist and antagonist activities depending on the specific tissue type and on the relative ER subtype interactions. Consequently this class of agents has been called selective estrogen receptor modulators or SERMs. As with phytoestrogens, SERMs appear to possess the ability to suppress prostate carcinogenesis. Toremifene has been evaluated in a phase IIa exploratory trial in men with high-grade PIN (Steiner and Pound, 2003). After 4 months of treatment with a daily oral dose of toremifene, 18 men with high-grade PIN underwent a repeat prostate biopsy. The prostate biopsy specimens showed significantly less high-grade PIN than historical controls. This trial provided the proof-of-concept support behind a currently open 485 patient placebo controlled, randomized dose finding phase IIb/III clinical trial (Price et al., 2006). This trial is investigating the efficacy of toremifene in reducing prostate cancer incidence in men with high-grade PIN. Men with high-grade PIN are treated for 12 months with placebo or toremifene and will undergo a repeat prostate biopsy at 6 and 12 months (the trial details are available at <http://www.gtxinc.com/tech/clinical.htm>). In addition, the National Cancer Institute is evaluating the effects of toremifene *versus* placebo in men with prostate cancer prior to radical prostatectomy. The objective of this phase II clinical trial is to evaluate the effects of a toremifene on biomarkers of prostate cancer. The trial details are available at <http://www.cancer.gov/search/ViewClinicalTrials>.

Difluoromethyl ornithine

DFMO is an irreversible inhibitor of ornithine decarboxylase involved in the synthesis of polyamines; it possesses cytostatic and cytotoxic effects (Messing et al., 1999). At the clinical level, interest in exploring DFMO as a chemoprevention agent for prostate cancer has recently increased as the administration of DFMO at 0.5 g/m² daily for 4 weeks to men scheduled for surgical interventions to treat either prostatic hyperplasia or neoplasia resulted in reduction of polyamine pools, including spermine (Simoneau et al., 2001). These results confirm that DFMO reaches the target tissue and hence may warrant further study as a possible chemopreventive agent for prostate cancer.

Vitamin D

Epidemiological studies have suggested that an increased prostate cancer risk is associated with decreased production of vitamin D. Studies in experimental models of prostate cancer have shown that the biologically active form of vitamin D, (1 α , 25-D₃) inhibits proliferation of human prostate cancer cells through mechanisms that include cell cycle arrest, induction of apoptosis and altered activation of growth factor signaling. Population based studies with vitamin D and studies of plasma 1,25 dihydroxy- and 25 hydroxyvitamin D levels have not provided any significant data supporting a protective effect of vitamin D in prostate carcinogenesis (Packianathan et al., 2004). Furthermore, the use of vitamin D analogs in humans has been limited by their hypercalcemic effects, but newer analogs with more tolerable toxicity are currently being tested in phase I and II trials. The NCI sponsored clinical trial with calcitriol, an active form of vitamin D, is ongoing and the details are available at <http://www.cancer.gov/search/ViewClinicalTrials>.

Soy isoflavones

Soy isoflavones have been identified as dietary components that may play an important role in reducing the incidence of prostate cancer. Various soy isoflavone supplementation regimens in prostate cancer patients have shown no statistically significant changes in serum PSA levels (Kumar et al., 2004). A prospective study of 12,395 men from Seventh Day Adventists in California demonstrated that frequent consumption of soy milk (at least daily) was associated with a 70% reduction in the risk of developing prostate cancer (Jacobsen et al., 1998). No large-scale clinical trials using soy or soy-based products as chemopreventive agents in prostate cancer have been reported.

Lycopene

Prospective case-control studies and meta-analysis of observational studies have shown that tomato products may play a role in the prevention of prostate cancer (Kirsh et al., 2006). It is hypothesized that lycopene may be one of the components of tomato which contributes to this association. Lycopene has been shown to be present in the human prostate at significant concentrations, a finding that supports the plausibility of a direct effect on prostate biology (Khachik et al., 2002). Recent studies on men with prostate cancer given supplements of lycopene-enriched products or tomato products for several weeks prior to radical prostatectomy demonstrated that lycopene

concentrations in the prostate could change rapidly in response to dietary intake and induce apoptotic cell death along with modulations in oxidative stress and tumor biology markers. It is unclear whether observed apoptotic effects are due to lycopene itself or some byproduct of this agent. A phase II randomized clinical trial of 15 mg of lycopene supplementation twice daily for 3 weeks before radical prostatectomy exhibited a decrease in the plasma IGF-I levels with no significant changes in Bax and Bcl-2 (Kucuk et al., 2001). Another study of the use of tomato oleoresin extract containing the equivalent of 30 mg/day of lycopene extract for 3 weeks before radical prostatectomy substantially reduced prostate volume in prostate cancer patients (Kucuk et al., 2002). Randomized trials to evaluate the efficacy of lycopene are still on going. The trial details are available at <http://www.cancer.gov/search/ViewClinicalTrials>.

Green tea catechins

Epidemiological and case-control studies have garnered support for the chemopreventive properties of green tea (Jian et al., 2004). A recent study was conducted on 60 volunteers with high-grade prostate intraepithelial neoplasia, a putative precursor of prostate adenocarcinoma (Bettuzzi et al., 2006). Patients received green tea compounds in capsule form 200 mg three times per day. Following 1 year of treatment, only 3% of patients that received the green tea polyphenols were diagnosed with cancer compared with 30% in the placebo group. Furthermore, patients that received the green tea capsules exhibited a longer latency to tumor detection and exhibited an improved quality of life. Another phase II study, in which 6 g/day of tea was administered to 42 patients with asymptomatic, androgen-independent prostate cancer, has demonstrated that a single patient achieved a PSA response of >50% that lasted for approximately 1 month. These patients suffered with side-effects that include diarrhea, nausea and fatigue (Jatoi et al.,

2003). Another clinical study used 250 mg dose of green tea polyphenols twice daily. In this study, 6 out of 19 patients had disease control for 3 to 5 months and there was only 1 patient whose PSA rise was affected by green tea supplementation. The dose used in this study did not discernibly alter the course of hormone-refractory prostate cancer (Choan et al., 2005). These results suggest that green tea possesses cancer chemopreventive properties and minimal anti-neoplastic activity against advance-stage prostate cancer.

Agents in preclinical evaluation on prostate cancer chemoprevention

A number of new and promising pharmaceutical and natural dietary agents are also under evaluation in preclinical settings. A list of these agents and their potential targets is shown in Table 3.

Combination strategies in prostate cancer chemoprevention

Prostate cancer chemoprevention in high-risk cohorts is still at an early stage of development, but it is already recognized that prevention by a single agent will be limited by both toxicity and potency issues. The combination approach using multiple agents with different mechanism(s) of action is an exciting new area of investigation. By the use of carefully chosen combinations of such agents, beneficial effects may result from exploiting their synergistic effects. Ongoing combination trials include the SELECT trial, using a combination of selenium and vitamin E; EUROSCAN, acetylcysteine and retinol; piroxicam and DFMO; future trials with DFMO and sulindac have been proposed (Meyskens, 2000). The results obtained from these combination trials will hopefully provide a better understanding of the mechanisms of action of these agents and will assess

Table 3
Promising pharmaceutical and dietary agents and their molecular targets in prostate cancer chemoprevention

Agents	Targets
Bicalutamide, dutasteride, finasteride	Anti-androgens (inhibitors of 5AR and AR)
Selenium, vitamin E, lycopene, resveratrol, tea polyphenols, sulfuraphane, curcumin, silibinin	Antioxidant/Detoxification
COX-1/COX-2 (NSAID), selective COX-2 (celecoxib), diindolylmethane, resveratrol, R-furbiprofen, lyprinol, sulindac sulfone, sulfuraphane	Arachidonic acid modulators, apoptosis inducers, NF- κ B, HETE and PGE-2 inhibitors
Daidzein, genistein, lignans, PC SPES	Phytoestrogens and inhibitors of ER- β , 5AR, AR and RTK
Arimidex, faslodex, raloxifene, toremifene	Anti-estrogens and inhibitors of ER- α/β , aromatase
Vitamin D analogs, targeetin, phenylbutyrate	Differentiation agents (VDR/RXR, HDAC)
Gene-based vaccines, tea polyphenols	Inhibitors of p53, Rb, PSA, PSMA
DFMO, polyamine analogs, panretin	Anti-proliferative agents, inhibitors of ODC, RXR/RAR
EGFR-Iressa, cKit-STI-571, VEGFR/PDGFR-SU-6668	Receptor tyrosine kinase modulators
FTI-276, SCH 66336, perillyl alcohol, D-limonene	Ras/falnesyl transferase modulators
Angiostatin, endostatin, 2-methoxyestradiol thalidolnide	Anti-angiogenesis modulators
Glitazones, DHEA analogs, retinoids, NSAIDs, 15d-PGJ2	PPAR modulators
Tamoxifen, vitamin D, lycopene, 4HPR, apigenin	IGF-I/IGFBP-3 modulators
Atrasentan, celecoxib, Bowman-Birk inhibitor	Growth factor modulators (ET-1, IL-6)
Vitamin D, zinc, SERMS	Telomerase modulators

5AR, 5 α -reductase; AR, androgen receptor; ER, estrogen receptor; NSAID, nonsteroidal anti-inflammatory drugs; NF- κ B, nuclear factor-kappaB; RTK, receptor tyrosine kinase; VDR, vitamin D receptor; RXR, retinoic acid receptor; HDAC, histone deacetylase; Rb, retinoblastoma; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; ODC, ornithine decarboxylase; RAR, retinoic acid receptor; PPAR, peroxisome proliferators-activated receptor; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; ET, endothelin; IL, interleukin; SERMS, selective estrogen receptor modulators.

whether such combinations are more efficacious than single agents.

Conclusions

In recent years, there has been a great deal of research directed at the prevention of prostate cancer. The recent completed prevention trial on prostate cancer (PCPT) suggests that long-term preventive use of biologically active agents may be associated with unforeseen and possibly adverse biological effects. Clearly the risks and side-effects of chemopreventive agents must be weighed carefully against the potential cancer preventive benefits. The PCPT trial emphasizes that cancer chemoprevention trials are not easy to design or interpret and that test agents that appear promising in observational studies may not prove to be as beneficial as expected when evaluated in randomized clinical trials. To ensure that all adverse effects of chemopreventive agents are detected, randomized controlled trials need to be carefully monitored for sufficient periods of time. Despite these challenges in chemoprevention, research continues to reveal clues into the molecular biology of disease and more opportunities for disease prevention are being recognized, particularly for prostate cancer. Recent advances in molecular targeted research designed to identify signaling pathways that might be targeted by chemopreventive agents may lead to the development of 'smart agents' capable of preventing or delaying the onset of prostate cancer, and ultimately reducing the burdens that this malignancy imposes on society.

Future prospects

The future of cancer chemoprevention will be based on continuing progress in discovering and implementing these approaches in the following areas:

- Development of agents that precisely target molecular events involved in carcinogenesis.
- The discovery of new agents which are effective, safe, free of undesirable side-effects and usable over relatively long periods of time.
- The coordinated efforts of scientists, biotechnologist, geneticists and physicians in advancing this area of investigation.
- Better definition of individual risk profiles, such as lifestyle and nutritional habit, correlating these aspects with possible chemoprevention strategies.
- More complete evaluation of the efficacies of combinations of chemopreventive agents, minimizing their dosages and side-effects while maximizing their salutary effects.

Overall, the challenges in cancer chemoprevention research are considerable but the potential rewards are enormous.

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