



Review Article

Chemoprevention of prostate cancer: Natural compounds, antiandrogens, and antioxidants — *In vivo* evidence

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Abstract

Prostate cancer is the leading non-skin malignancy detected in US males and the second cause of death due to male cancer, in the US. Interventions with drugs or diet supplements that slow down the growth and progression of prostate cancer are potentially very effective in reducing the burden of prostate cancer, particularly if these treatments also prevent the *de novo* development of new prostatic malignancies. Challenges to identify efficacious agents and develop them for chemopreventive application in men at risk for prostate cancer have included uncertainty about which preclinical models have the ability to predict efficacy in men and lack of consensus about which early phase clinical trial designs are the most appropriate and cost-effective to test promising agents. Efficacy studies in animal models have identified several agents with potential chemopreventive activity against prostate cancer, but few of these findings have been translated into clinical trials. This article identifies some of the major issues associated with prostate cancer chemoprevention research and summarizes the most significant current results from animal efficacy studies and human clinical prevention trials. This summary focuses on: (1) Naturally occurring agents and compounds derived from such agents, including green tea and its constituents, silibinin and milk thistle, and genistein and soy, (2) chemoprevention drugs including agents interfering with androgen action, and (3) antioxidants such as selenium, vitamin E, and lycopene. The general lack of activity of antioxidants is discussed, followed by considerations about translation of preclinical chemoprevention efficacy data, focusing on dose, form, bioavailability, and timing of administration of the agent, as well as discussion of study design of clinical trials and the predictive ability of preclinical models.

Keywords: Animal models, antioxidants, chemoprevention, clinical trials, natural compounds, prostate cancer

INTRODUCTION

Prostate cancer is the leading non-skin malignancy detected in US males and the second cause of death due to male cancer,

in the US.^[1] The disease typically develops and progresses slowly over a period that may include decades. There are reports indicating that about 30% of US men between the ages of 20 and 40 years have microscopic size cancers in their prostate.^[2] Thus, interventions with drugs or diet supplements that slow down the growth and progression of these small tumors are potentially very effective in reducing the burden of prostate cancer, particularly if these treatments also prevent the *de novo* development of new prostatic malignancies.^[3,4] The challenge has been to identify efficacious agents and to develop them for chemopreventive application in men at risk

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for prostate cancer. One problem is the uncertainty about which preclinical models have the ability to predict efficacy of agents in men. Another difficulty has been the lack of consensus about which early phase clinical trial designs are the most appropriate and cost-effective to test promising agents, before embarking on hugely expensive, large, randomized prevention clinical trials, with cancer detection as endpoint.

Several approaches have been used to select candidate agents for efficacy testing. One approach is to select agents that have been active for other cancer sites, but with a few exceptions this has not been very successful. Efficacy studies in animal models have identified several agents with potential chemopreventive activity against prostate cancer,^[5] but few of these findings have been translated into clinical trials. The purpose of this article is to identify some of the major issues associated with prostate cancer chemoprevention research and to provide a summary of the most significant current results from animal efficacy studies and human clinical prevention trials, but not to provide an exhaustive summary of all such studies. There are many studies on the effects of various compounds on the growth of prostate cancer cells *in vitro* or when xenografted into immunodeficient mice. Such cell models are useful for studying the molecular mechanisms of chemoprevention agents. However, they are relevant to therapy, but not prevention, as the vast majority of these models involve cells derived from metastatic prostate cancer deposits and none reflect the early stages of prostate carcinogenesis, and will not be discussed here.

NATURALLY OCCURRING AGENTS AND COMPOUNDS DERIVED FROM NATURALLY OCCURRING AGENTS

Green tea and its constituents

Green tea polyphenols have been reported to inhibit tumor development in the so-called transgenic adenocarcinoma of the mouse prostate (TRAMP) model,^[6] but unpublished data from other investigators suggest that this finding has been difficult to reproduce and may be restricted to prevention of early stage tumors and treatment that begins before the onset of puberty.^[7,8] Partly published studies with other *in vivo* prostate cancer models using rats, in our laboratory, were uniformly negative for green tea extract.^[9,10] The activity of green tea polyphenols in the TRAMP model may be related to the known inhibitory effects of the green tea catechin epigallocatechin-3-gallate (ECGC) on the activity of the enzyme 5 α -reductase, which converts the male sex hormone testosterone to the active androgen 5 α -dihydrotestosterone.^[11] Also, the expression and activity of the androgen receptor is attenuated by green tea polyphenols and catechins.^[8,12,13] The expression and

activity of the oncogenic SV40-large and small T antigens (SV40-Tag) in the TRAMP model are targeted to the prostate by the probasin gene promoter, which is under the control of the androgen receptor. Therefore, it is probable that the green tea polyphenols interfered with the expression of the SV40-Tag at a critical moment and, thereby, prevented the oncogenic events to take place in this model.^[14] Consistent with this notion, protein expression of SV40-Tag was not detectable in the prostate of TRAMP mice that did not develop tumors following ECGC treatment, but was detectable in those prostate tumors that were not prevented by this agent,^[15] although others^[8] did not find effects of ECGC on the protein expression of SV40-Tag in the TRAMP model. The major drawbacks of the TRAMP model are its aggressiveness and the predominantly neuroendocrine phenotype of the tumors that develop, which are not frequent in humans, who mostly develop adenocarcinomas.^[16] Lesions in this model, that resemble high-grade prostate intraepithelial neoplasia (PIN) found in the human prostate, do not appear to progress to adenocarcinoma,^[16] casting some doubt on the relevance of the TRAMP model.

A randomized placebo-controlled clinical trial of 12 months intervention, with a green tea catechin mixture (600 mg / day), was conducted in men with elevated prostate-specific antigen (PSA) and high-grade PIN on biopsy, but no cancer. Follow-up biopsies at 6, 12, and 24 months were carried out in the treatment arm (n = 30, 30, and 13, respectively) and the placebo arm (n = 30, 24, and 9, respectively). A statistically significant reduction in the detection of prostate cancers, from 30 to 3.3% at 12 months and 53 to 11% at 24 months, was found in the treated men compared to men on placebo.^[17,18] On account of the small number of subjects, the short duration of this trial, and the inherent sampling problems associated with prostate biopsies, these findings should be considered preliminary and await reproduction. In summary, there are mixed findings from animal studies about the preventive efficacy of green tea and its constituents, while there are human data suggestive of the protective activity of green tea catechins against prostate cancer. Further human studies are needed to firmly establish whether green tea can prevent prostate cancer.

Silibinin and milk thistle

Silibinin derived from Silybin or extract from the milk thistle plant has been shown to inhibit prostate tumor formation in the TRAMP model,^[19] but this effect appeared to be limited to inhibition of the growth of established prostate neoplasms late in the process of tumor progression.^[20,21] This suggests that the effects of silibinin in the TRAMP model are more of a therapeutic nature than chemopreventive. Importantly,

silibinin did not appear to reduce the expression of the SV40-Tag.^[19] On basis of these findings and the absence of toxic or carcinogenic effects of milk thistle,^[22] a small placebo-controlled phase I/II clinical trial with a silibinin-containing milk thistle preparation was conducted in men, prior to radical prostatectomy for prostate cancer.^[23] Although the dose of this preparation was high (a total of 13 g ingested daily for two weeks), most of the six treated subjects reported only mild grade 1 or 2 adverse events; one subject experienced a postsurgical grade 4 thromboembolic event, which may have been associated with the treatment. No adverse events were reported for the six control subjects. Serum concentrations of silibinin reached 20 – 23 μM , but tissue levels were extremely low, ranging from undetectable to no more than 0.5 nM. There were no effects of the treatment on serum levels of IGF-1 and IGFBP-3, nor were there effects on the labeling index for Ki-67 and caspase-3 and COX-2 positive cells in prostate tissue. These human data do not provide support for the notion that silibinin or milk thistle prevent prostate cancer.

Genistein and soy

We and others have shown that dietary exposure to soy isoflavones, the Bowman-Birk protease inhibitor occurring in soy, and whole soy protein inhibit prostate carcinogenesis induced by carcinogens plus hormones in adult rats and in the TRAMP mouse model and a similar rat model.^[24-32] However, there are reports that in the TRAMP model the major soy isoflavone genistein at lower, nutritionally relevant, doses stimulated carcinogenesis and greatly enhanced metastatic capacity.^[33,34] Clearly, both the dose and form of the agent as well as probably the timing of administration are critical determinants for whether genistein, and by inference soy, have cancer-preventive effects or enhance prostate cancer development. The anti-cancer effects of genistein have been attributed to its known inhibitory effects on tyrosine kinase, topoisomerase II, 5 α -reductase, and angiogenesis, and its activation of several growth factor receptor pathways, but most of these effects, particularly those on tyrosine kinase activity, occur only at non-physiologically high concentrations.^[35-38] At low, physiological concentrations genistein binds to both the estrogen receptors (ER)- α and - β , with a greater affinity for ER- β , and genistein is thought to probably exert some or most of its effects through ER- β .^[39] How genistein might elicit proliferative, rather than anti-proliferative effects on prostate cancer cells at low doses is uncertain. Genistein also has an antioxidant activity (see later in the text) and may inhibit carcinogenesis via protection of cells against oxidative stress.^[35,40-42] The other major soy isoflavone, diadzein, is far less biologically active. Daidzein, but not genistein, is converted to equol by intestinal microbes in 30 – 60% of humans, a phenomenon

that appears to be quite stable within a given individual.^[43,44] This daidzein metabolite has significant estrogenic and anti-androgenic activities, including prostatic effects in rats.^[45-47] It is conceivable that the chemopreventive activity of soy isoflavones may differ in men who produce equol and those who do not and that is related to the hormonal properties of equol,^[44] but this has not been explored to date.

There are several reports of placebo-controlled clinical trials with soy products, often enriched for isoflavones. In healthy men (i.e., men without detected prostate cancer) soy does not seem to affect the serum levels of PSA.^[48,49] Also, in men with a rising PSA after local radiation or surgical therapy, soy does not appear to significantly affect the serum PSA levels,^[50-52] which we confirmed [Bosland, unpublished data]. Studies on the effects of soy on PSA without placebo control or cross-over designs and trials with complex mixtures containing soy have also been reported,^[53-57] but are not discussed here, because their results are difficult to interpret. Most interesting are the few studies, reported to date, on changes in prostate tissue biomarkers following intervention with soy in placebo-controlled trials, but unfortunately there is no clear pattern of changes that has yet emerged.^[58-60] In a placebo-controlled clinical trial with men diagnosed with high-grade PIN on biopsy, a supplement mixture of selenium and soy (exact preparation was not defined for either in the article) was provided for three years, together with alpha-tocopherol, but the cumulative incidence of prostate cancer was not affected,^[57] casting doubt on the ability of soy to affect prostate cancer development.

Other naturally occurring agents

There is a large literature on the potential to prevent or treat prostate cancer with vitamin D or vitamin D analogs,^[61] but there is increasing evidence to dispute this notion,^[62,63] and there is the problem of toxicity of vitamin D and analogs that limit their application in humans. A 1,25(OH)₂D₃ analog has not been active when given mixed into the diet in a TRAMP-like mouse model,^[64] but systemic administration of 1,25-D₃ inhibited the development of PIN-like lesions in mutant mice lacking both *Pten* and *Nkx3.1* genes.^[65] There are no other animal studies with appropriate models and we will not further discuss vitamin D chemoprevention here. Curcumin, derived from turmeric, has *in vitro* properties that are consistent with cancer inhibiting activity, but it is poorly bioavailable *in vivo*.^[66] Nonetheless, dietary curcumin inhibited tumor development in the TRAMP model, as did phenylethylisocyanate (PEICT), which occurs naturally in cruciferous and other vegetables.^[67] However, in a chemically induced rat prostate cancer model, dietary curcumin has not been active.^[68] Resveratrol, which occurs in grape seeds and red wine inhibited late stage tumor development in TRAMP

mice,^[69] and had marginal inhibitory activity in a similarly aggressive SV-40-based model in rats.^[70] Pomegranate extracts and juice have anticancer-like activity in cell models, but has not been tested *in vivo*.^[71] None of these substances have been tested in human studies.

CHEMOPREVENTION DRUGS

Agents interfering with androgen action

Agents interfering with androgen action, such as androgen receptor blockers or 5 α -reductase inhibitors, have been very effective in preventing prostate cancer development in most, but not all, appropriate animal models.^[5,72-74] The 5 α -reductase-type 2 inhibitor finasteride and 5 α -reductase-type 1 and 2 inhibitor dutasteride have each been tested in a large clinical trial, named the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride in Prostate Cancer Events (REDUCE) trial, respectively.^[75,76] In both of these studies, a reduced risk of developing prostate cancer by 23 – 24%, over a four-to-seven-year intervention period, was seen in men at average risk of prostate cancer (finasteride) or high risk men (dutasteride).^[77,78] Both agents exerted the strongest preventive effect on low-grade prostate cancer, whereas, for high-grade cancer there was no protective effect in the dutasteride trial (Gleason score 7 or higher) and a small, but significant, increased risk in the finasteride trial (Gleason score 8 or higher). These findings have been hotly debated in the literature and explanations for the increased risk of high-grade cancer in the finasteride trial have been developed.^[79-81] Neither agent is currently approved by the US FDA for the prevention of prostate cancer, and a long-term follow-up of finasteride study participants is still ongoing which will allow to observe their response to hormone ablation therapy, if recurrence develops. Nevertheless both studies do provide evidence in support of androgen action as an important and biologically plausible potential target for chemoprevention of prostate cancer.

Other drugs

Dehydroepiandrosterone (DHEA), which is strongly inhibitory in mammary cancer models, also inhibited prostate cancer induction in rats with a combination of chemical carcinogen treatment (methylnitrosourea) and long-term, low-dose testosterone administration, via slow release Silastic implants.^[82] Fluasterone, a non-hormonally active fluorinated analog of the androgen precursor DHEA, was also inhibitory in the latter model.^[83] One of the most active inhibitory compounds was the pan-retinoic acid receptor (RAR and RXR) agonist 9-*cis*-retinoic acid, which reduced prostate cancer incidence in the above-mentioned rat model by more than 70%.^[84] Unfortunately, 9-*cis*-retinoic acid is too toxic to be considered for application in humans in a prevention

setting and Fluasterone is currently not available for clinical studies. The retinoid-like agent *N*-(4-hydroxyphenyl)all-*trans*-retinamide (4-HPR) was not efficacious in this rat model,^[85] and in two small clinical trials no evidence was found of its protective activity.^[86,87]

ANTIOXIDANTS

Oxidative stress generating reactive oxygen species (ROS) has the potential to cause oxidative DNA damage and has been associated with the causation of human cancer, including prostate cancer.^[88-90] One mechanism by which ROS may be produced and leads to cancer is inflammation, which has been implied in the etiology of several major human malignancies, including prostate cancer.^[91,92] Basic research and many epidemiological studies have suggested the cancer preventive activity of several antioxidants. This notion has been the basis of the hypothesis that dietary antioxidants may prevent cancer, which has been tested in several randomized clinical trials (RCTs) and preclinical model studies. The ability to prevent lung cancer of beta-carotene, which quenches ROS, and alpha-tocopherol (vitamin E), that interferes with ROS-induced lipid peroxidation, has been tested in an RCT with smokers. However, beta-carotene increased the risk of lung cancer,^[93] although this adverse effect disappeared after a longer follow-up.^[94] Vitamin E did not protect against lung cancer in this study, but reduced the risk of prostate cancer in smokers.^[93] Selenium is an essential component of a range of selenoproteins. Several of these proteins have an antioxidant activity or are involved in antioxidant mechanisms and detoxify ROS, such as glutathione peroxidase (GPx), which acts either alone or in combination with other enzymes, such as superoxide dismutase (SOD).^[95,96] In a clinical trial of subjects with an increased risk for skin cancer, the ability to prevent such tumors of selenium in the form of a selenium-rich yeast dietary supplement was tested. It did not prevent, but slightly increased the risk of non-melanoma skin cancer, while the risk of colon and particularly prostate cancer was reduced.^[97-99]

Selenium and vitamin E

As the above-mentioned RCTs suggested preventive activity of selenium and vitamin E for prostate cancer as a secondary endpoint, the ability to prevent prostate cancer was evaluated in a very large RCT, the Selenium and Vitamin E Cancer Prevention Trial (SELECT). However, selenomethionine, one of the forms of selenium in the human diet, and alpha-tocopherol either alone or in combination did not have a preventive activity.^[100] In a much smaller RCT of men with high-grade PIN on biopsy, subjects were provided for three years with a mixture of selenium and soy (exact preparation was not defined for either in the article)

together with alpha-tocopherol or with placebo, but no preventive effect was observed on the cumulative incidence of prostate cancer.^[57] Using two animal models, we tested the ability of selenomethionine, selenized yeast, alpha-tocopherol, and combinations thereof, to prevent prostate cancer, but we did not detect any preventive activity of these agents.^[101,102] However, there is epidemiological and animal model evidence to suggest that not alpha tocopherol, but gamma-tocopherol, the major tocopherol in the human diet,^[103] might be protective against prostate cancer.^[104,105]

Lycopene

Lycopene, a very strong ROS-quenching antioxidant present in tomatoes, water melons, and other vegetables / fruits, has been associated with reduced risk of prostate cancer in some epidemiological studies, but not in several others and the overall evidence for a protective effect of lycopene is very limited at best.^[106] Lycopene was negative in two rat models using a carcinogen plus testosterone protocol for prostate cancer induction^[107,108] and in a chemically-induced prostate cancer model in rats,^[68] but tomato powder increased prostate cancer-specific survival in rats treated with carcinogen plus testosterone (the effect of lycopene or tomato powder on tumor incidence was not assessed in this study).^[108] In contrast, feeding lycopene, but not tomato paste, from four to twenty weeks of age inhibited the development of prostate tumors in TRAMP mice, but did not affect the weight of the prostate complex.^[109] Adding lycopene to a diet containing supplemental selenium and vitamin E, retarded tumor development in a mildly aggressive TRAMP-like mouse model (LADY) and reduced the expression of the oncogenic SV-40 transgene, which may explain its tumor inhibitory effect.^[110] Thus, the results of most animal studies appear to indicate a lack of preventive activity of lycopene. There are no reports yet of lycopene tested in a RCT with prostate cancer as the endpoint. However, lycopene may have antioxidant-like effects in the human prostate; feeding a lycopene-rich tomato sauce reduced the level of oxidative DNA damage in the prostate in one Phase II study, but a lycopene-rich tomato extract did not do so in another study from the same group.^[111-113] Consumption of lycopene-rich tomato sauce also increased apoptosis in prostate tissue and reduced serum PSA in one of these studies.^[111] Other clinical trials are ongoing.

Considerations

There are probably many reasons why antioxidants may have such diverse effects and did not prevent cancer in several studies; some of the more important reasons include:

- It has been proposed that some or many antioxidants have biphasic effects that differ at lower and higher doses.^[114-116]
- There are diverse mechanisms by which antioxidants exert

their antioxidant effect that may, in part, be affected by genetic polymorphisms in genes encoding for antioxidant proteins, which may lead to different effects in different people exposed to the same antioxidant dose.^[90,117-119]

- Many antioxidant agents have biologically significant effects of a non-antioxidant nature and are known or likely to interact with each other. For example we found that at low, physiologically relevant concentrations, selenium can stimulate *in vitro* proliferation of prostate cancer cells, while it inhibits cell proliferation and indices of apoptosis only at higher concentrations; effects that are probably not related to its incorporation in antioxidant selenoproteins.^[120]
- A critical issue is the dietary supply of antioxidants before intervention with these agents is started in RCTs and animal studies. For example, in the aforementioned RCT with selenized yeast, the risk of prostate cancer was only reduced in men who had low baseline selenium levels.^[121] Data on this issue from the SELECT trial are not (yet) available. In most animal studies, baseline diets were fully selenium-sufficient and supplementation might not have increased the antioxidant status further.^[85, 101] Indeed, we did not discover that selenomethionine prevented oxidative DNA damage or that it induced expression or activity of GPx or SOD antioxidant enzymes in such an experiment with rats [Ozten and Bosland, unpublished data].
- For selenium, another important issue is the dietary forms of this agent that are studied, because they can differ in bioactivation pathways.^[122] Selenium has different forms, including various organoselenium compounds such as selenomethionine, Se-methylselenocysteine, and methylseleninic acid, which does not naturally occur, as well as inorganic selenium compounds such as selenite.^[123] Each form can trigger different metabolic pathways, leading to differences in their cancer suppressing activity.^[124]
- There are many dietary factors that have significant antioxidant activity, in addition to their major biological effects, even though they are not commonly considered antioxidants. The soy isoflavone genistein is one such factor that has substantive antioxidant activity, through ROS scavenging and via up-regulation of the expression and activity of antioxidant enzymes at physiologically relevant doses,^[35,40-42] whereas many of its other potential anticancer properties, such as tyrosine kinase inhibition, may predominate only at unrealistically high dietary levels.^[35,36]

In conclusion, important antioxidants are likely to have highly non-linear dose-response relationships with respect to their anticancer activity and to have significant interactions with factors that are difficult or impossible to control in RCTs and even animal studies, but substantially modify antioxidant efficacy. Most troubling is the possibility that some

antioxidants at physiologically achievable doses may have adverse, cancer-enhancing activity that may unpredictably vary among humans.

TRANSLATION OF PRECLINICAL CHEMOPREVENTION EFFICACY DATA

For translation of preclinical chemoprevention data to human testing in randomized clinical trials, several critical issues need to be considered, such as dose, form, and bioavailability of the agent, timing of treatment, clinical trial design, and predictive value of the preclinical models. The agent dose in preclinical studies is usually 40 – 80% of the maximally tolerated dose, but in humans lower doses may be required by regulatory agencies or deemed prudent by investigators. Naturally occurring chemoprevention agents are also often tested in animal models at doses higher than those physiologically relevant in humans, which may have different, sometimes potentially harmful effects. A recent report on such biphasic effects of genistein in preclinical models suggests the potential for harm at low, physiologically relevant doses.^[34] The form of the agent used in animal studies, often mixed into the diet, may not be feasible in humans, for whom administration in tablets or capsules is typically used. The bioavailability of some agents with considerable *in vitro* cancer-inhibitory activity is poor, such as is the case for curcumin.^[66] In addition, there is very little information about the bioavailability of any agent to the relevant target, prostate tissue. Only for lycopene are there data in this respect, but the metabolism of this and other compounds may be complex and result in the presence of metabolites with unknown activity in prostate tissue.^[113] Thus, preclinical studies and subsequent RCTs must be coordinated, such that both form and bioavailability of the agents tested are considered and agent metabolism is addressed as well. Importantly, the timing of agent administration in animal studies and human clinical trials typically differs considerably; chemopreventive treatment of humans is typically not considered until middle age. Therefore, delayed administration of the agent under test must be included in the preclinical research phase, which has been proven feasible.^[82] For some agents, such as green tea polyphenols and genistein, preventive activity in preclinical models has only been identified when treatment occurred early in life,^[7,8] which is obviously not feasible in humans.

Other important issues in translating preclinical data pertain to the study design of clinical prevention trials.^[3,125,126] Following Phase I safety studies, short-term Phase II studies, with agent administration before radical prostatectomy, are needed, to further establish safety and generate data on efficacy using relevant intermediate end-points in the prostate tissue. Beyond the Phase II studies, trials of intermediate

duration are needed prior to embarking on large Phase III studies. Several study designs have been proposed, most of which are applied to populations at high risk for prostate cancer, such as men with elevated PSA, but negative biopsies, men with high-grade PIN, but no cancer on biopsy, or men with a family history of prostate cancer.^[3,125,126] One such type of intermediate trial involves treatment of men with recurring prostate cancer, with reduction in the rise of PSA in these men as the end-point.^[3,125,126] The problem with this study design is that one cannot differentiate between the effects of the test agent on prostate cancer cell growth and effects on PSA expression, which are not necessarily linked and can even occur in opposite directions. One other intermediate trial design involves treatment of men at high risk of recurrence after radical prostatectomy.^[3] This design not only includes a relatively low sample size (250 – 300 subjects) and short duration (two to three years of treatment), but focuses on prostate cancer that is clinically significant and potentially lethal. This is important because many prostate cancers currently detected in the USA have questionable or low clinical significance and may not need to be prevented. Thus, clinical trials that focus on clinically significant prostate cancer are crucial in developing chemopreventive agents that are active against aggressive, potentially lethal forms of prostate cancer. However, no such studies have been completed to date. Of note, two of the currently completed Phase III RCTs for the chemoprevention of prostate cancer, SELECT and PCPT, involve average risk men, whereas participants of the REDUCE trial had elevated risk of prostate cancer associated with elevated PSA levels. In one other RCT with men at increased risk of prostate cancer because of the presence of high grade PIN on biopsy, but no cancer^[127], the antiestrogen toremifene did not significantly reduce prostate cancer development in three years of follow-up [<http://prostatecancerinfolink.net/risk-prevention/prevention-prostatecancer/other-trials/>]. In all four studies, the majority of detected cancers were likely of low clinical significance but not distinguishable from potentially lethal cancers.

Predictive ability of preclinical models

The ability of preclinical models to predict the outcome of subsequent clinical trials is one of the most important issues in the translation of preclinical chemoprevention data. Preclinical studies of selenium and vitamin E, with rat models, have been uniformly negative, as indicated earlier, and were thus fully predictive of the negative outcome of SELECT. Similar preclinical model studies with antiandrogens^[73,74] were also predictive of the reduction in prostate cancer development in the PCPT and REDUCE trials with 5 α -reductase inhibitors.^[77,78] Tamoxifen was not active in preventing prostate cancer in a rat model study,^[74] predictive of the lack of significant efficacy of the antiestrogen

toemifene. The predictive value of animal models for other chemoprevention agents is not clear because of the lack of definitive clinical trials. The limited clinical trials with silibinin, green tea polyphenols, lycopene, soy, and 4-HPR are insufficient to allow a formal definitive evaluation of the predictive ability of preclinical animal models for these agents.

CONCLUDING REMARKS

A well-coordinated and concerted effort to developing chemoprevention agents for prostate cancer, by applying a rational approach to translating relevant and reproducible preclinical data to validated clinical trials, focusing on agents that hold substantial promise, will be essential for producing preventive treatments that are substantially active against clinically significant disease without the potential for harm. Bioavailability of agents for the prostate, and systemic and prostatic metabolism of agents, may be critically important, but remains underappreciated, as there are few pertinent data from both preclinical models and human clinical trials. Antioxidants have not emerged as being active against prostate cancer development, while several naturally occurring agents have not been moved forward in translational approaches. Agents that target androgen mechanisms have reduced detection of prostate cancer, but it is uncertain whether these compounds reduce prostate cancer-specific mortality or significantly slow the disease progression. Other agents have met with a poorly coordinated approach to their development as chemopreventives and/or have been tested in limited or inconclusive clinical trials. Problems in this regard are: (1) Negative results (i.e., lack of activity) and potentially harmful effects of candidate agents are often not published, (2) chemoprevention is often not considered profitable by the pharmaceutical and food industries, limiting targeted investment, and (3) funding agencies are hesitant to put together cohesive and well-coordinated approaches to chemopreventive agent development, relying instead on investigator-initiated approaches that, almost by definition, are doomed to be uncoordinated. In addition, prostate cancer is a highly heterogeneous disease at the molecular level, impeding targeted chemopreventive drug development. Moreover, most chemopreventive agents have multiple complex activities that can be profoundly non-linear in relation to dose and interaction with other factors, of both genetic (e.g., polymorphisms in critical genes) and environmental nature (e.g., diet). Finally, prostate cancer, as a disease, presents us with some additional problems that pose significant challenges to designing chemoprevention clinical trials and interpreting their results: (a) Most prostate malignancies clinically detected in the US and other western countries are not clinically significant, in the sense that they do not lead to cancer-specific mortality; (b) the prevalence

of microscopic-size prostate cancers often of doubtful clinical significance is very high in middle-aged and older men around the world; and (c) at present, it is difficult to differentiate clinically significant from insignificant cancers in a majority of the cases. The good news is that some of the currently available preclinical models appear to be predictive of the outcome of clinical trials and will provide useful data for the development of rational approaches to the chemoprevention of prostate cancer.

NOTE ADDED IN PROOF

In a just published article, dietary supplementation of healthy men with vitamin E was reported to significantly increase risk of prostate cancer in the SELECT study, with a hazard ratio of 1.17 (99% confidence interval 1.004-1.36; $P = 0.008$).^[128]

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