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Future directions in the prevention of prostate cancer

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Abstract

The high global incidence of prostate cancer has led to a focus on chemoprevention strategies to reduce the public health impact of the disease. Early studies indicating that selenium and vitamin E might protect against prostate cancer encouraged large-scale studies that produced mixed clinical results. Next-generation prostate cancer prevention trials validated the impact of 5 α -reductase inhibitors in hormone-responsive prostate cancer, and these results were confirmed in follow-up studies. Other interventions on the horizon, involving both dietary and pharmacological agents, hold some promise but require further investigation to validate their efficacy. In this Review, we discuss the clinical and preclinical evidence for dietary and pharmacological prevention of prostate cancer and give an overview of future opportunities for chemoprevention.

Introduction

Prostate cancer is the most common cancer in American men, affecting one in six during his lifetime.¹ The disease is ubiquitous, present in a growing fraction of men as they age; as life expectancy increases, this cancer will become responsible for raising the number of cancer deaths in men.^{2,3} Unfortunately, patients are generally asymptomatic until their disease becomes metastatic. Although a range of new agents have been developed for advanced-stage prostate cancer, treatment is expensive, is associated with a host of adverse effects and most men with metastatic prostate cancer will ultimately die of their disease.

In response to this challenge, serum prostate-specific antigen (PSA) testing became highly prevalent in the late 1980s. Current US guidelines regarding PSA screening vary, but the 2013 American Urological Association Guideline recommends screening between ages 55 years and 69 years, as this seems to be the age during which individuals gain the greatest benefit from screening.⁴ Although prostate cancer mortality has certainly fallen after PSA screening was introduced because cancers were being detected at an earlier stage, the unintended consequence has been a high rate of overtreatment of indolent disease. As treatment is expensive—and frequently has a significant impact on a man's urinary, sexual

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and gastrointestinal quality of life⁵—screening was deemed inappropriate by the US Preventive Services Task Force in 2012.⁶

Consequently, chemoprevention has been increasingly emphasized as an approach to mitigate the prostate cancer burden and the issues surrounding the overtreatment of indolent disease. Chemoprevention is defined as the use of drugs, vitamins or other agents to try to reduce the risk of—or delay the development or recurrence of—cancer.⁷ In prostate cancer, chemopreventive strategies have initially focused on sensitivity to androgens, although interest has grown in attempting to find inhibitors of chronic inflammation as this process is involved in tumour growth, angiogenesis and chemoresistance (Figure 1). In this Review, we discuss the clinical and preclinical data available for a range of chemoprevention options in prostate cancer, including the outcomes for studies assessing both dietary and pharmacological agents. We also give an overview of future opportunities for chemoprevention in this disease.

Lessons from phase III trials

Selenium and vitamin E supplementation

Substantial preclinical and epidemiological evidence has pointed to the potential of two agents—selenium and α -tocopherol (vitamin E)—that might reduce the risk of prostate cancer.^{8–10} Thought to exert protective effects by virtue of their anti-inflammatory activities, promising results were observed from secondary analyses of randomized clinical trials.^{9,11} In the Nutritional Prevention of Cancer Trial, sponsored by the National Cancer Institute (NCI), 1,312 patients who had had skin cancer were randomly assigned to receive 200 μ g of elemental selenium per day in the form of high-selenium yeast.⁹ The primary end point of this study was a subsequent skin cancer and, although no reduction in skin cancer incidence was noted, a 63% reduction in subsequent prostate cancer was noted in those patients receiving selenium. In the Alpha Tocopherol Beta Carotene study¹¹ (with a primary end point of lung cancer incidence), again sponsored by the NCI and conducted in Finland among smokers, new prostate cancer incidence was reduced by 32% and mortality by 41% in patients receiving vitamin E. On the basis of these compelling data, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) trial was initiated by the NCI in 2001.¹⁰ In this study, 35,534 healthy men over the age of 50 years and from all races were randomly assigned to receive selenium (200 μ g/day of L-selenomethionine), vitamin E (400 IU daily), both agents (at the same doses used for each single-agent arm) or placebo in a 2 $\times$ 2 study design. Initial findings of a preplanned interim analysis (median follow-up of 5.5 years) showed that daily selenium and vitamin E supplements, either taken alone or together, did not prevent prostate cancer. These findings led to cessation of administration of both agents, but monitoring of the participants continued. In a follow-up analysis that included 54,464 additional person-years of continued observation and found 521 more prostate cancers, this group reported—on the basis of a recommendation from the independent data and safety monitoring committee—a significant increase in the risk of prostate cancer of 17% (odds ratio [OR] 1.17; 99% CI 1.04–1.36) in the vitamin E-only group compared with those not receiving vitamin E.¹² The results from this study suggest that neither selenium nor vitamin E likely have an impact on reducing prostate cancer incidence in the US population.

Some unanswered questions remained at the end of the SELECT study. Could the lack of effect from selenium be attributed to the fact that only a small number of men might be deficient in this nutrient?¹³ Why was no significant increase in risk of prostate cancer seen in the combination (vitamin E plus selenium) group? What effect would a lower dose of vitamin E have? Could the type of selenium used in the trial (selenomethionine) have blunted the effect of the agent?¹⁴ Certainly, other doses of vitamin E could have a potentially different effect, but given that the dose of 400 IU was carcinogenic, it is unlikely that a large study would be conducted to examine the effect of a lower dose. Additional confirmation of the lack of efficacy of selenium was provided by a randomized trial that enrolled 619 men with highgrade prostatic intraepithelial neoplasia, 423 of whom were randomly assigned to receive either selenium or placebo. In this study, selenium at a dose of 200 µg/day as selenomethionine had no effect on the subsequent risk of prostate cancer.¹⁵

5α-reductase inhibitors

Prostate cancer is unequivocally an androgen-modulated disease. Circulating testosterone that enters prostatic cells is converted to dihydrotestosterone (DHT) by 5α-reductase. Although both testosterone and DHT can then bind to the androgen receptor, ultimately resulting in nuclear transcription, DHT has a greater affinity and a slower rate of dissociation from the androgen receptor than testosterone, making 5α-reductase a target for prevention and treatment of prostate-related diseases.¹⁶ Testosterone at high concentrations interacts with the human androgen receptor in a similar way to DHT. Although the role of androgens in prostate carcinogenesis is less clear than their role in progression and treatment, a host of observations in the early 1990s suggested that modulation of the androgen axis could affect prostate cancer risk.¹⁷ With the development of finasteride, the first 5α-reductase inhibitor (5-ARI) for the treatment of urinary symptoms associated with benign prostatic hypertrophy, the Prostate Cancer Prevention Trial (PCPT) was initiated to determine if the risk of prostate cancer could be reduced by this agent. A total of 18,882 men with serum PSA levels <3.0 ng/ml were randomly assigned to receive finasteride or placebo.¹⁸ Treatment was continued for 7 years, and all participants who were cancer-free at this point were recommended to undergo prostate biopsy. More than 1 year before the planned study completion date, the independent data and safety monitoring committee recommended early closure because of overwhelming evidence that the primary objective (prostate cancer prevalence) had been met. A relative risk (RR) reduction for prostate cancer of 24.8% with finasteride was observed compared with those in the placebo group (95% CI 18.6–30.6%, $P<0.001$; 803 of 4,368 participants in the finasteride group versus 1,147 of 4,692 participants in the placebo group).¹⁸ However, this seemingly positive result was marred by an increased number of participants who developed high-grade (Gleason 7–10) tumours in the finasteride group: 280 of 757 (37%) versus 237 of 1,068 (22%) in the placebo group ($P<0.001$). Since that time, *post hoc* analyses have demonstrated that the increase in high-grade cancer was attributable, at least in part, to improved cancer detection in patients treated with finasteride through improved sensitivity of serum PSA, digital rectal examination and prostate biopsy for prostate cancer detection; in the cases of PSA and biopsy, sensitivity for detection of high-grade cancer was also improved with finasteride.¹⁹ Follow-up analysis of men in the PCPT, the longest randomized trial of this medication to date, also revealed a significant reduction in the risk of prostate enlargement complications in those patients treated with finasteride.²⁰

This observation suggests a dual prevention benefit among men who are developing symptoms of prostate enlargement: reduction in the risk of prostate cancer as well as in the risk of complications related to prostate enlargement.

The results of the long-term follow-up of the PCPT have recently been reported.²¹ With up to 20 years of follow-up data in an analysis of all 18,880 eligible men, prostate cancer was found in 989 of 9,423 (10.5%) men in the finasteride group, compared with 1,412 of 9,457 (14.9%) in the placebo group, which translates to a risk reduction of 30% (RR in finasteride group 0.70; 95% CI 0.65–0.76; $P<0.001$). Although an increased risk of Gleason 7–10 prostate cancer remained in the finasteride group (RR 1.17; 95% CI 1.00–1.37; $P=0.05$), no difference in survival between the finasteride and placebo-treated patients was apparent when stratified by grade. These data confirm that finasteride is associated with a significant reduction in the risk of prostate cancer and, despite a greater number of high-grade tumours diagnosed in the finasteride group, no excess deaths were observed in patients treated with this agent. This observation suggests that men who have opted for PSA testing might achieve similar survival outcomes, but with 30% fewer cancers diagnosed if finasteride is used.

There are two isoenzymes of 5 α -reductase; finasteride inhibits the type 2 isoenzyme, which is the most important in the prostate. An even greater reduction in DHT levels can be achieved by dual inhibition of both isoenzymes with, for example, the inhibitor dutasteride. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial investigated the preventive impact of dutasteride in 8,231 men with a PSA level 2.5–10.0 ng/ml and a previous negative biopsy. The results were similar to the PCPT: a 22.8% (95% CI 15.2–29.8; $P<0.001$) reduction in risk of prostate cancer was observed in the dutasteride treatment arm. Gleason 7–10 tumours were slightly more common in the dutasteride group (220 out of 3,299 patients in the dutasteride arm versus 233 out of 3,407 patients in the placebo group, $P=0.81$).²² Of concern in this study was the increase in Gleason score 8–10 tumours in study years 3 and 4, rising from one tumour in the placebo group to 12 tumours in the dutasteride group ($P=0.003$). Ideally, long-term follow-up study of this population, as carried out for the finasteride update, would clarify whether this excess of 13 Gleason 8–10 tumours is biologically relevant when compared with the 1,517 total tumours detected over the course of the trial.²¹

Taking into account that >200,000 men are diagnosed with prostate cancer in the USA annually,¹ a one-quarter reduction in prostate cancer risk using a 5-ARI, an agent that also reduces the risk of prostate enlargement symptoms and complications (such as urinary retention and need for surgical treatment), would have a tremendous public health impact. Further analysis of the PCPT and REDUCE studies should shed light on whether the increase in detection of high-grade disease was an artefact, and an ongoing large case–control study might help us understand which men stand to benefit the most from 5-ARIs.²³ In this study, genetic variants of *SRD5A2* (the polymorphic gene that encodes for 5 α -reductase), among others, are being examined for their influence on prostate cancer risk and the impact of finasteride as a cancer prevention intervention.²⁴

Other preventive opportunities

Inflammation blockade

The role of acute and chronic inflammation in the genesis of prostate cancer remains controversial; however, accumulating evidence indicates anti-inflammatory blockade provides a major opportunity for chemoprevention in this disease (Figure 1). Irritation to the prostate has been postulated to come from three potential sources: infection, dietary stimulation of prostanoid secretion and hormonal changes.²⁵ Increasingly, proliferative inflammatory atrophy (PIA) of the prostate, a condition characterized by elevated markers of inflammation, is being recognized as preceding prostatic intraepithelial neoplasia (PIN) and prostate cancer.²⁶ With long-term stimulation, NF- κ B induces the expression of *PTGS2* (which encodes cyclooxygenase 2 [COX-2]) and generates many downstream effectors that tip the balance toward an inflammatory state.²⁶ Elevated levels of cytokines and chemokines hasten the process, aided and abetted by suppressed vitamin D receptor levels—itsself a master regulator of inflammation—and elevated mTOR signalling, resulting in a sustained stimulus to angiogenesis and chemoresistance. Both *in vitro* and *in vivo* models of prostate cancer have demonstrated the antiproliferative and antitumour potential of vitamin D3 both in chemopreventive and chemotherapeutic studies.^{27–30} Ongoing clinical trials investigating the effects of vitamin D3 supplementation in patients with low-risk and localized prostate cancer are being conducted.^{31,32}

A range of factors have been postulated to contribute to prostatic inflammation, including bacterial infection (by *Escherichia coli* or *Propionobacter acnes*)²⁶ and dietary factors, such as polyunsaturated fats—sources of arachidonic acid—that are involved in prostanoid biosynthesis and inflammation.³³ Inflammatory cells (leukocytes and T lymphocytes) are frequently detected in prostate tumours; for example, in the REDUCE trial, 80% of patients had evidence of inflammation in biopsies.³⁴ In another study, men of African American origin were found to have more inflammation in prostate tumours than those not of African American descent.³⁵ Indeed, archived prostate tissues subjected to microarray gene-expression analysis revealed that specimens from African American men had elevated expression of interleukin (IL)-1 β , IL-6, IL-8 and chemokine receptor type 4 (CXCR4) in prostate tissues compared with prostate tissue from white American men.³⁶ A meta-analysis of 11 prospective cohorts with 194,796 patients revealed a link between elevated levels of C-reactive protein (CRP), indicative of systemic inflammation, and increased risk of cancer in general, as well as lung cancer specifically; CRP level was possibly indicative of breast, colorectal and prostate cancer.³⁷ Urine reflux has also been hypothesized to have a role in the expression of inflammation markers and elevated levels of cytokines, although whether this is a common risk factor remains unclear.³⁸ Finally, animal studies have shown that inflammation is a critical early step in the progression to prostate cancer, and Mimeault and Batra³⁹ suggest that elevated levels of TGF- β , CXCR1, CXCR2, CXCL8, NF- κ B and IL-17 are possible contributors to this process.

A number of additional agents have shown promise as preventive agents for prostate cancer. Some of these agents will soon enter clinical testing, whereas some have not yet reached the level of evidence required for their use in the clinic as chemopreventive agents.

Lycopene

Considerable evidence suggests that a high dietary intake of fruit and vegetables is associated with a reduced risk of many cancers, including prostate cancer.⁴⁰ In this arena, the chemopreventive activity of lycopene and soy isoflavones is being investigated; the earliest hypotheses proposed that the protective mechanism of these and similar agents is the result of their antioxidant properties.⁴¹

Antioxidants protect cells against free radicals that can damage DNA, and as free radical damage increases with age, lycopene (a carotenoid found in red fruit and vegetables) could protect against age-related cancers, such as prostate cancer.⁴² On the basis of published cohort studies and a meta-analysis of six high-quality case-control studies, the American Institute for Cancer Research concluded that “foods containing lycopene probably protect against prostate cancer.”⁴³

Despite promising retrospective studies, prospective studies have been less-supportive of the protective role of lycopene. In the largest of these studies, the PCPT, lycopene intake was not associated with a reduction in the risk of prostate cancer among 9,559 men who completed the trial.^{24,44,45} Additionally, no relationship was detected between lycopene serum concentrations and risk of prostate cancer. Similarly, in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which included approximately 28,000 men, serum lycopene levels were not related to risk of subsequent prostate cancer after 1–8 years of follow-up (OR 1.14; 95% CI 0.82–1.58 for highest versus lowest quintile; *P* for trend of 0.28).⁶ To determine the clinical efficacy of lycopene, the physiologically effective dose must be delineated, more-potent analogues must be synthesized, combinatorial studies with enhancers must be conducted and administration regimens must be optimized.^{46–49} Ongoing phase II clinical trials are examining the preventive effect of lycopene in tandem with other antioxidants to reduce the size of prostate cancers, prevent the recurrence of prostate cancer, or augment therapy,⁵⁰ and completed clinical trials might provide more insight into the therapeutic potential of lycopene. However, at this juncture, a considerable amount of preparatory research is needed before lycopene can truly be considered a promising avenue in prostate cancer prevention.

Soy foods

Soy-based foods, such as tofu and miso, contain isoflavones that are phytoestrogens. The two most abundant isoflavones that have been extensively studied mechanistically are genistein and daidzein. Evidence suggests that in countries where soy consumption is a culinary mainstay, such as most of Southeast Asia, the incidence of prostate cancer is lower than in North America.⁵¹ A meta-analysis of five cohort and eight case-control studies that investigated the relationship between soy food consumption and the risk of prostate cancer suggested that high consumption of some soy-based foods can significantly decrease the risk of prostate cancer.⁵² A number of small clinical studies also examined the relationship between the intake of soy foods and prostate cancer risk. In one such study, 100 Japanese men who had undergone prostate biopsy and were found to be cancer-free were randomly assigned to receive soy isoflavones (40 mg; comprised of 66% daidzein, 24% glycitin and 10% genistein) and curcumin (100 mg) or placebo for 6 months. No difference was observed

in PSA levels between the two treatment groups (initial PSA levels were 8.0 ± 6.7 ng/ml in the placebo group versus 10.5 ± 9.5 ng/ml in the treatment group; PSA levels posttrial were 7.1 ± 5.6 ng/ml in the placebo group versus 7.4 ± 4.6 ng/ml in the treatment group).⁵³ In another study, 58 men at risk of prostate cancer (defined as men with preneoplastic lesions) or with low-grade prostate cancer received one of three types of soy protein (either soy protein isolate, alcohol extracted soy isolate or soy milk isolate) for 6 months. Fewer cases of prostate cancer were reported in men who had received soy protein ($P=0.01$), although tissue biomarkers were not affected.⁵⁴ Several studies have focused on modulation of PSA as a short-term indicator of the health benefits of soy. In a study of 47 patients who were scheduled for radical prostatectomy, patients were randomly assigned to receive placebo or genistein (30 mg daily) for 3–6 weeks before surgery. Testosterone levels decreased by 7.8% in patients receiving genistein, whereas serum PSA levels increased by 4.4% in patients who received placebo.⁵⁵ In a randomized trial of vitamin E, selenium and soy protein in men ($n = 303$) with high-grade PIN, the combination of agents had no effect on progression to prostate cancer.⁵⁶

Animal models of prostate cancer have been used to explore the effects of specific soy isoflavones on prostate cancer. For example, in a study using the transgenic adenocarcinoma of the mouse prostate (TRAMP model), mice were fed control diets or diets containing genistein (250 mg genistein per kg chow).⁵⁷ TRAMP mice fed genistein exhibited reduced prostatic cell proliferation compared with those on the control diet; downregulation of ERK signalling was a possible explanation for this observation. Other murine studies have provided conflicting results, for example, showing inhibition of prostate cancer at one dose of genistein but stimulation of metastasis at a lower dose.⁵⁸ A xenograft study in athymic mice in which animals were fed a control or genistein-supplemented diet showed that the metastatic potential of the tumours was increased.⁵⁹ Although these mixed results cast doubt on the chemopreventive promise of genistein, the data do imply that further studies are needed to identify which soy foods, if any, should be recommended for clinical use in prostate cancer prevention.^{49,60} Furthermore, a combination of soy components or consumption of whole soybeans might have a greater preventive effect than supplementation with individual components alone.⁶¹ Even if preclinical data for combining soy components with other natural agents (such as green tea or lycopene) are compelling, trials testing these regimens would need to be conducted.

Future opportunities for prevention

In addition to the chemopreventive efforts already discussed, the pathways involved in the progression of prostate cancer still afford many additional opportunities for chemoprevention (Figure 1). These include natural products, such as curcumin, and drugs currently used in other populations, such as metformin in patients with diabetes mellitus.

Curcumin

Curcumin is the major polyphenol component of the Indian spice turmeric (*Curcuma longa*), and has been extensively studied for cancer prevention (Table 1).⁶² Its anti-inflammatory activity has been confirmed in a wide variety of tumour types, including prostate, head and

neck and mammary tumours.⁶³ One clinical study, in 85 patients with previous negative prostate biopsies, showed that a supplement combining soy and curcumin reduced serum PSA levels sharply in those with initial PSA readings of >10 ng/ml.⁵³

In vitro studies have shown that curcumin interferes with a number of components of cell signalling pathways dysregulated in prostate cancer, including COX-2, NF- κ B, Bcl-XL, AKT and receptor activator of NF- κ B ligand (RANKL).^{64–67} These effects, as well as modulation of a number of chemokines and cytokines, suggest that inflammatory components in prostate cancer development or progression could be targeted with curcumin. Promising data also indicate that curcumin, by acting as a kinase inhibitor, could inhibit prostate cancer metastasis by targeting cytokines CXCL1 and CXCL2 through inhibition of NF- κ B.⁶⁸ Studies have also shown that curcumin might be effective in castration-resistant prostate cancers; one study has showed that curcumin potentiates the effect of paclitaxel therapy in androgen-independent DU 145 cells by circumventing absorption problems when complexed in a polymer.⁶⁹

Despite numerous studies supporting the anticancer properties of curcumin, its clinical use has been restricted because of its low bioavailability and poor tissue absorption.^{63,70} Several approaches have been undertaken to overcome these limitations, including synthesis of structural analogues, adjuvant agents (for example, piperine which improves bioavailability by increasing the solubility of curcumin in blood)^{71,72} and development of delivery systems (for example, nanoparticles, nanoemulsions and liposomes).^{72–75}

Green tea and green tea polyphenols

Studies in animal models have shown that green tea prevents prostate cancer (Table 2) through a mechanism of action that includes targeting apoptosis by preventing the degradation of p53.^{76–85} A meta-analysis of 13 studies involving 3,608 men with prostate cancer among 111,499 individuals revealed a protective relationship between prostate cancer and the long-term intake of green tea, mostly in Asia where the intake of green tea is common.⁸⁶

Polyphenon E is a mixture of green tea-based polyphenols that has been used in clinical studies of chemoprevention for breast, leukaemia and prostate cancer. In an open-label, single-arm, two-stage phase II clinical trial, 26 men with positive prostate biopsies were given daily doses of polyphenon E (800 mg/day) for 3–6 weeks until ungoing radical prostatectomy. Polyphenon E administration lowered serum levels of hepatocyte growth factor (HGF), VEGF, insulin-like growth factor-binding protein 3 (IGF-BP3), insulin-like growth factor 1 (IGF-1) and PSA in these patients.⁷⁹ In another study, 60 men with high-grade PIN were randomly assigned to receive green tea catechins (in pill form) or placebo for 1 year.⁸⁵ Although a small trial, patients receiving the polyphenols had a significantly reduced progression of high-grade PIN to cancer compared with those who received placebo ($P<0.01$). However, this rapid inhibition of high-grade PIN might be attributable to sampling error rather than the intervention, and a confirmatory trial with more patients is required before a definitive conclusion can be reached.

Metformin

Metformin is the most widely prescribed biguanide worldwide for control of blood sugar levels in patients with type 2 diabetes mellitus (T2DM).^{87,88} Metformin might be a promising agent worthy of rigorous clinical assessment for prostate cancer prevention given the collateral benefits attributed to the drug's glucose control mechanism—such as reducing the risk of cardiovascular disease and polycystic ovary syndrome—and its low toxicity profile. Indeed, a number of clinical studies have suggested that metformin might also reduce the risk of prostate cancer (Table 3). Lehman *et al.*⁸⁹ examined metformin, sulfonylurea and statin use in >5,000 men with T2DM in the Veterans Affairs (VA) Healthcare System, hypothesizing that these agents have synergistic protective effects in prostate cancer. Metformin was associated with a 31% reduction in the risk of prostate cancer, but only in men receiving statins; the risk of cancer was more than twofold less than observed in those not receiving any intervention ($P<0.0001$). Importantly, only 10% of the cohort was taking both metformin and statins; thus, this finding must be validated in larger studies. Other clinical studies have produced mixed results; a similar protective effect on prostate cancer has been shown in some studies, but these results have been contradicted in two meta-analyses of metformin use in patients with T2DM.^{90–98} Metformin use does have a low risk of nausea, diarrhoea and loss of appetite, which might limit application in some settings. Finally, although few studies of metformin and prostate cancer have been conducted using animal models, studies of other tumour types—notably in models of oral, ovarian and pancreatic cancer—have shown a chemopreventive effect for metformin.^{99–101} Metformin has been found to inhibit the growth and progression of xenografted LnCaP prostate tumours in mice.¹⁰²

NSAIDs

The epidemiological evidence linking aspirin and other NSAIDs to protect against prostate cancer is still equivocal (Table 4), but growing in favour of possible use.^{41,103–106} Studies have included cohort and case–control studies and secondary analyses of large-scale clinical trials. For example, one case–control study, comparing 9,007 men diagnosed with prostate cancer with men without prostate cancer, showed aspirin conferred a 10% reduction in risk of prostate cancer (OR 0.90, 95% CI 0.81–0.95); this benefit was associated with >10 years of NSAID use.¹⁰⁷ A meta-analysis of studies reported in the mid-2000s showed a 39% reduction in the risk of prostate cancer with aspirin, but not with ibuprofen.¹⁰⁸ Using data from the PLCO study, investigators found a reduction of approximately 10% (OR 0.91, 95% CI 0.84–0.99) in prostate cancer risk with aspirin use, whereas, again, ibuprofen use did not confer a benefit.¹⁰⁹ Aspirin has been available much longer than other NSAIDs, such as ibuprofen and naproxen, and as time passes it is likely that similar benefits to aspirin will become evident for these NSAIDs.

Not all studies have demonstrated a benefit for NSAID use in prostate cancer chemoprevention. In the PCPT, use of NSAIDs increased the risk of benign prostate hyperplasia (OR 1.21, 95% CI 1.01–1.46).¹¹⁰ A Finnish study of 24,567 case–control pairs gathered between 1995–2002 from a national registry of recorded prescription drug use reported an increase in risk of overall and advanced-stage prostate cancer in men who used NSAIDs, but aspirin use was associated with a reduced risk of prostate cancer.¹¹¹ By

contrast, Rothwell *et al.*¹¹² did not find a protective association of aspirin for prostate cancer risk (OR 0.94; 95% CI 0.82–1.08), but did observe potential protection for other tumour types. In this literature review of case–control and cohort studies published from 1950 to 2011, regular use of aspirin was associated with reduced risk of colorectal cancer (pooled OR 0.62, 95% CI 0.58–0.67, $P<0.0001$, 17 studies), with little heterogeneity ($P=0.13$). Similarly, consistent reductions were observed in risks of oesophageal, gastric, biliary and breast cancer. That the authors found inconsistent results for other tumour types might be explained by less-detailed recording of aspirin exposure, a lack of updating of exposure between initial recruitment and subsequent diagnosis of cancer and by a lack of adjustment for imbalances in baseline clinical characteristics.

Few animal studies investigating the relationship between NSAIDs and prostate cancer prevention have been conducted. Most studies have examined the effects of celecoxib—a selective COX-2 inhibitor—on PC3 or LnCaP xenografts, either alone or in combination with other treatments (such as androgen ablation or atorvastatin).^{113–115} In general, these interventions have reduced progression of prostate cancer.

Resveratrol

Pigments naturally found in fruits and vegetables also hold promise for prostate cancer prevention (Table 5). One such pigment is resveratrol—a phytoalexin found abundantly in red grapes, raspberries, plums, blueberries and red wine.^{42,60,66,116–118} Similar to curcumin, several preclinical studies have shown that resveratrol inhibits prostate cancer metastasis or enhances sensitivity of otherwise radioresistant PC3 cells to radiation.^{119–123} Indeed, resveratrol significantly inhibits the incidence of high-grade PIN in mice, but has paradoxically been shown to reduce survival of mice with LAPC4 human prostate cancer xenografts; in LnCaP xenografts, survival was not untowardly affected.^{124–126} The implications of these different results in LnCaP and LAPC4 models are unclear. However, the therapeutic efficacy of resveratrol is limited owing to its low bioavailability and extensive metabolic clearance.^{127,128} Different drug delivery systems, analogues and compound co-administration are being investigated to enhance the pharmacokinetic properties of resveratrol.^{129–132}

Phase I clinical trials on the effects of resveratrol in healthy volunteers and in patients with colorectal cancer and hepatic metastases demonstrated an acceptable safety profile.^{133,134} However, a phase II study of resveratrol (SRT501) in 24 patients with relapsed or refractory multiple myeloma was suspended because of a high rate of adverse effects, especially renal toxicity.¹³⁵ Notably, patients with multiple myeloma generally exhibit renal impairment or insufficiency, which might explain the observed high nephrotoxicity in this trial.^{135–137} Renal toxicity might not be observed in a healthier population, or in populations without this susceptibility; indeed, studies of resveratrol in otherwise healthy men should be performed to confirm if renal toxicity is a specific adverse effect of resveratrol observed in patients with multiple myeloma.

Conclusions

Of the many chemopreventive strategies that have been explored in prostate cancer, only 5-ARIs are supported by compelling clinical evidence. Although an increased risk of high-grade disease observed with 5-ARIs initially tempered enthusiasm for this approach, the long-term evidence of safety and a further reduction in risk should reinvestigate consideration of this class of agents for most men at risk of prostate cancer. Studies indicate that vitamin E should not be used as it is associated with an increased risk of cancer. These two examples go some way to illustrate the nuances (and importance) of large-scale clinical trials of prostate cancer prevention; no clinical recommendations should be made unless agents are tested in an appropriately powered and designed randomized trial. Despite the practical difficulties of conducting large trials with thousands of participants, preclinical and clinical data (from small studies) strongly support the exploration of various agents to reduce the risk of prostate cancer. A challenge for the future will be the translation of preclinical data into clinically useful strategies, which will require very large sample sizes on a par with those of the PCPT and SELECT studies.

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Key points

- Chemoprevention has been increasingly explored to mitigate the global burden of prostate cancer and the overtreatment of indolent disease that has arisen in the prostate-specific antigen (PSA) screening era
- Preclinical and epidemiological evidence suggested that selenium and α -tocopherol (vitamin E) might reduce the risk of prostate cancer
- A large trial found vitamin E to significantly increase the risk of prostate cancer and selenium to have no effect on risk
- The strongest evidence supports the use of 5 α -reductase inhibitors for prostate cancer prevention, with recent data showing that the risk reduction with these agents is 30%

Review criteria

We searched for original articles focusing on prostate cancer and prevention in the MEDLINE and PubMed databases published between 1960 and 2013. The search terms we used were “prostate cancer”, “prevention”, “chemoprevention”, “diet”, “inflammation”, “clinical trials”, “animal” and “human studies”. All papers identified were English-language full-text papers. We also searched the reference lists of identified articles for further papers.

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Figure 1.

Prostate cancer progression. Accumulated DNA damage, oxidative damage, genetic polymorphisms and chronic inflammation all contribute to disease progression. These events also provide opportunities for possible intervention with chemopreventive agents.

Abbreviations: COX-2, cyclooxygenase 2; IL, interleukin; miR, microRNA; mTOR, mammalian target of rapamycin; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen.

Table 1

Preclinical evidence for preventive activity of curcumin in prostate cancer

Study	<i>In vitro</i> model	Findings	<i>In vivo</i> model	Findings	Putative mechanism(s)
Sundram <i>et al.</i> (2012) ⁶⁴	LNCaP, LNCaP C4-2 and PC3	Inhibition of cell proliferation, colony formation and cell motility; Enhanced cell–cell aggregation in prostate cancer cells	LNCaP C4-2 xenograft in athymic nude mice	Inhibition of tumour growth correlated with enhanced membrane localization of β -catenin	Activation of PKD1, resulting in changes in β -catenin signalling and inhibition of β -catenin transcription activity; Enhanced β -catenin levels in PCa cells; Decreased active cofilin levels
Shankar <i>et al.</i> (2008) ^{65 *}	LNCaP	No <i>in vitro</i> -specific results	LNCaP xenograft in Balb/c nude mice	Inhibition of tumour growth, metastasis and angiogenesis; Induction of apoptosis; Upregulation of TRAIL receptors; Inhibition of activation of NF- κ B and its gene products	Sensitization of LNCaP cells by inducing death receptors, upregulating proapoptotic proteins, inhibiting antiapoptotic Bcl-2 proteins and inducing expression of cell-cycle inhibitors
Slusarz <i>et al.</i> (2010) ⁶⁶	TRAMP-C2 and PC3	Inhibition of cell growth	C57BL6/J TRAMP	Reduction and delay in prostate cancer initiation	Inhibition of Hedgehog signalling pathway
Barve <i>et al.</i> (2008) ^{67 ‡}	NA	NA	C57BL6 TRAMP	Decreased incidence of prostate tumour formation; Inhibition of PIN; Decreased cellular proliferation; Increased apoptotic index	Downregulation of AKT signalling pathway to decrease cell proliferation

* Curcumin and TNF-related apoptosis-inducing ligand.

‡ Curcumin and phenylethylisothiocyanate.

Abbreviations: NA, not applicable; PIN, prostatic intraepithelial neoplasia; PKD1, polycystic kidney disease 1 protein; TRAIL, TNF-related apoptosis-inducing ligand; TRAMP, transgenic adenocarcinoma of mouse prostate.

Table 2

Evidence for preventive activity of green tea in prostate cancer

Study	Intervention	Study design	Findings
Preclinical			
Hsu <i>et al.</i> (2011) ⁸⁰	Soy protein, green tea or both	<i>In vivo</i> ; noble rat model (hormone-induced prostate cancer model)	Soy protein or green tea alone had insignificant effects; Soy protein and green tea suppressed NF- κ B p50 binding activity and protein levels; Decreased prostate inflammatory infiltration; Increased Bax:Bcl-2 ratio and decreased prostate hyperplasia
Adhami <i>et al.</i> (2009) ⁸¹	Green tea polyphenol infusion (0.1% w/v)	<i>In vivo</i> ; TRAMP model	Inhibition of IGF-1 and its downstream targets (PI3K/AKT, pERK) in animals with PIN
Siddiqui <i>et al.</i> (2008) ⁸²	Green tea polyphenol infusion (0.1% in drinking water)	<i>In vivo</i> ; TRAMP model	Reduction of NF- κ B, IKK- α , IKK- β , RANK, NIK and STAT3 expression; Induction of apoptosis
Clinical			
Nguyen <i>et al.</i> (2012) ¹³⁸	Polyphenon E containing 800 mg EGCG daily 3–6 weeks prior to surgery	Randomized, double-blind, placebo-controlled trial in men ($n = 48$) with prostate cancer scheduled to undergo radical prostatectomy in 3–6 weeks	Low to undetectable level of polyphenon E found in prostatectomy tissue; Favourable, but not statistically significant, changes in serum PSA, serum insulin-like growth factor axis and oxidative DNA damage in blood leukocytes in intervention arm; No differences in markers of cell proliferation, apoptosis and angiogenesis observed in prostatectomy tissue in the different treatment arms
McLarty <i>et al.</i> (2009) ⁷⁹	Daily polyphenon E containing 800 mg EGCG to a total of 1.3 g of tea-derived polyphenols until prostatectomy (median 34.5 days on treatment)	Open-label, single-arm, two-stage phase II clinical trial in men ($n = 26$) with positive prostate biopsies	Reduction in HGF, VEGF, PSA, IGF-1, IGFBP-3 and IGF-1:IGFBP-3 ratio with no elevation of liver enzymes

Abbreviations: EGCG, epigallocatechin-3-gallate; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; NA, not applicable; NIK, NF- κ B-inducing kinase; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; RANK, receptor activator of nuclear factor- κ B; STAT3, signal transducer and activator of transcription-3; TRAMP, transgenic adenocarcinoma of mouse prostate; VEGF, vascular endothelial growth factor.

Table 3

Evidence for preventive activity of metformin in prostate cancer

Study	Study design	Findings	Putative mechanism(s)	Clinical implications
Preclinical				
Colquhoun <i>et al.</i> (2012) ^{139*}	<i>In vitro</i> AR ⁺ LNCaP and AR ⁻ PC3; <i>In vivo</i> LNCaP murine xenograft	Additive effect of metformin on bicalutamide; Reduced clonogenicity with greater effects in AR ⁺ LNCaP cells; Reduced cell and tumour growth more pronounced with combination than with either monotherapy	LNCaP: activated pAMPK leading to reduced cell proliferation by decreasing phosphorylated mTOR expression and G1/S cell-cycle arrest; PC-3: enhanced apoptosis by increased Bcl-2-associated X protein and decreased caspase 3 expression	Potential role for metformin as an adjunct to androgen deprivation therapy and prostate cancer prevention agent
Ben Sahra <i>et al.</i> (2011) ^{140‡}	<i>In vitro</i> LNCaP; <i>In vivo</i> LNCaP murine xenograft	Approximately 96% inhibition of cell viability	Induction of p53-dependent apoptosis via AMPK pathway; Re-expression of functional p53 in p53-deficient prostate cancer cells; Arrested prostate cancer cells in G2/M independent of p53	Potential use as anticancer treatment
Ben Sahra <i>et al.</i> (2008) ¹⁴¹	<i>In vitro</i> DU145, PC3 and LNCaP; <i>In vivo</i> LNCaP murine xenograft	Inhibited cell proliferation by 50%, decrease of cell viability; Oral treatment led to 50% reduction of tumour growth; Intraperitoneal treatment led to 35% reduction of tumour growth	Blockade of the cell cycle at G0/G1 accompanied by strong decrease of cyclin D1 expression; Induction of Rb phosphorylation; Increase in p27 ^{Kip} expression; Strong reduction of cyclin D1 levels in tumours	Potential use as anticancer treatment
Clinical				
Lehman <i>et al.</i> (2012) ^{89§}	Men with T2DM (<i>n</i> = 5,042) without prior cancer and prescribed metformin or sulfonylurea as hypoglycaemic medication	Reduced prostate cancer incidence in patients on statins; Increased prostate cancer incidence in patients not on statins; Men on combination treatment had the greatest reduction in LDL levels	Synergistic effects between metformin and statin via lipid-lowering	Potential use of statins as prostate cancer prevention agent
Wright and Stanford (2009) ⁹⁰	US population-based case-control study of men aged 35–74 years with prostate cancer (1,001 cases and 942 controls)	In white men, metformin use resulted in 44% prostate cancer risk reduction; No association for black men	NR	Potential relationship between metformin, mTOR inhibition, and cancer prevention

* In combination with bicalutamide (antiandrogen therapy).

‡ In combination with 2-deoxyglucose.

§ In combination with statins (specific statins were not specified). Abbreviations: AR⁺, androgen-receptor-positive; AR⁻, androgen-receptor-negative; LDL, low-density lipoprotein; mTOR, mammalian target of rapamycin; NR, not reported; Rb, retinoblastoma protein; T2DM, type 2 diabetes mellitus.

Table 4

Evidence for preventive activity of NSAIDs in prostate cancer

Study	Intervention	Study design	Findings	Putative mechanism(s)
Preclinical				
Zhang <i>et al.</i> (2010) ¹¹³	SSA	<i>In vitro</i> LNCaP, LNCaP C4-2, TRAMP-C2; <i>In vivo</i> C57BL/6 TRAMP model	SSA suppressed growth of human and mouse prostate AR ⁺ cancer cells; Dietary SSA attenuated prostatic growth, suppressed AR-dependent glandular epithelial lesion progression via repressed cellular proliferation	Suppression of cell growth by G1 arrest at low concentration (<10 µmol/l); At higher concentrations (10 µmol/l), suppression associated with caspase-mediated apoptosis
Zheng <i>et al.</i> (2010) ¹¹⁵	Atorvastatin and celecoxib	<i>In vitro</i> LNCaP; <i>In vivo</i> androgen-independent LNCaP tumour xenograft in SCID mice	Atorvastatin or celecoxib inhibited growth and stimulated apoptosis; Combination was more effective than either agent alone; Mice treated with atorvastatin or celecoxib alone suppressed regrowth or LNCaP tumours after castration; Combined low-dose treatment exerted more-potent effect on growth inhibition and progression	Inhibition of cell proliferation and induction of apoptosis
Clinical				
Schenk <i>et al.</i> (2012) ¹¹⁰	NSAIDs (aspirin, ibuprofen, sulindac, meloxicam, nabumetone, celecoxib) aspirin and nonaspirin NSAIDs	Cohort study for risk of symptomatic BPH men without BPH at baseline (<i>n</i> = 4,735) using data from the placebo arm of the PCPT	No reduction in symptomatic BPH; NSAID use associated with increased BPH risk of 23%, with similar risks for aspirin (29%) and nonaspirin NSAID (34%); Modest association of NSAID use with increased risk of BPH, the result of confounding indications	Intervention on inflammatory pathways might reduce risk of BPH
Shebl <i>et al.</i> (2012) ¹⁰⁹	Aspirin and ibuprofen	Analysis of patient-reported aspirin and ibuprofen use in relation to prostate cancer risk in men aged 55–74 years in the PLCO study (<i>n</i> = 29,450)	Daily aspirin use, but not ibuprofen use, associated with reduced prostate cancer risk	Inhibition of COX; Suppression of cell proliferation; Induction of apoptosis
Mahmud <i>et al.</i> (2011) ¹⁰⁷	Aspirin, arylacetic acids, butylpyrazolidines, oxicams and propionates	Nested case-control study using data from SPDP and cancer registry to examine the effects of dose and duration of NSAIDs in men (<i>n</i> = 9,007 aged >40 years)	Any use of propionates (ibuprofen, naproxen) associated with modest reduction in prostate cancer risk; No clear evidence of dose-response or duration-response relationships for any NSAID	Inhibition of cell proliferation, COX and angiogenesis; Induction of apoptosis
Dhillon <i>et al.</i> (2011) ¹⁴²	Aspirin	Prospective cohort study of health professionals (40–75 years old) for long-term aspirin use (<i>n</i> = 51,529)	Men taking >two adult-strength aspirin tablets weekly had 10% lower risk of prostate cancer; For T3b, T4 and N1 disease, no significant associations with aspirin use; For M1 disease, men taking >six adult-strength tablets weekly had similar reductions in risk hazard ratio (HR 0.72, 95% CI 0.54–0.96)	Inhibition of cell proliferation and COX; Induction of apoptosis

Study	Intervention	Study design	Findings	Putative mechanism(s)
Salinas <i>et al.</i> (2010) ¹⁰⁵	Aspirin, ibuprofen and acetaminophen	US population-based case-control study of men aged 35–74 years (<i>n</i> = 1,001)	Reduction in prostate cancer risk (21%) in aspirin users compared with nonusers; Long-term aspirin (>5 years) and daily use of low-dose aspirin associated with decreased risk; Significant interaction with aspirin use for <i>PTGS2</i> rs12042763 polymorphism; Prostate cancer risk not associated with ibuprofen or acetaminophen use	Inhibition of cell proliferation, metastasis and PTGS enzymes; Induction of apoptosis
Coogan <i>et al.</i> (2010) ¹¹⁴	Statins (simvastatin, atorvastatin, lovastatin, fluvastatin, pravastatin, rosuvastatin) and NSAIDs (undefined)	Case-control study in men aged 18–79 years (<i>n</i> = 1,367)	No protective effect of statin use alone or in combination with NSAIDs on risk of advanced prostate cancer	NA

Abbreviations: AR, androgen receptor; BPH, benign prostatic hyperplasia; COX, cyclooxygenase; NA, not applicable; PCPT, Prostate Cancer Prevention Trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; *PTGS2*, gene encoding prostaglandin-endoperoxide synthase (PTGS) 2; SCID, severe combined immunodeficiency; SPDP, Saskatchewan Prescription Drug Plan; SSA, sulindac sulfide amide; TRAMP, transgenic adenocarcinoma of mouse prostate.

Table 5

Preclinical evidence for preventive activity of resveratrol in prostate cancer

Study	Intervention	Study design	Findings	Putative mechanism(s)
Klink <i>et al.</i> (2013) ¹²⁴	Resveratrol alone	<i>In vivo</i> LAPC4 xenograft and LNCaP xenograft in CB17SC SCID mice	Decreased survival in LAPC4 xenograft model; No change in survival in LNCaP xenograft model; Decrease in IGF-1 and increased in IGFBP-2 in both models	Upregulation of oncogenic pathways E2F3 and β -catenin in LAPC4 xenograft model but not in LNCaP xenograft model [*]
Ganapathy <i>et al.</i> (2010) ¹²¹	Resveratrol, TRAIL or both	<i>In vivo</i> PC3 xenograft in Balb/c nude mice	Inhibited growth of PC3 xenografts; Combination was more potent than either compound alone; Resveratrol alone upregulated TRAIL-R1, TRAIL-R2, Bax and p27; Resveratrol alone inhibited Bcl-2 and phosphorylation of FOXO3; Combination inhibited angiogenesis and markers of metastasis	Resveratrol potentially enhances apoptosis-inducing activity of TRAIL by activating FOXO3 and its target genes
Brizuela <i>et al.</i> (2010) ¹⁴³	Resveratrol alone	<i>In vitro</i> PC3, C4-2B; <i>In vivo</i> heterotropic PC3 xenograft in NMRI nude mice (PC3/SPHK1 and PC3/GFP)	Impeded cell growth <i>in vitro</i> and <i>in vivo</i>	Inhibition of SPHK1/SIP pathway
Slusarz <i>et al.</i> (2010) ⁶⁶	Resveratrol alone	<i>In vitro</i> TRAMP-C2 and PC3; <i>In vivo</i> C57BL/6J TRAMP model	Inhibited growth in human and mouse prostate cancer cell lines; Reduced or delayed prostate cancer in TRAMP mice	Inhibition of Hedgehog signalling pathway
Harper <i>et al.</i> (2009) ¹⁴⁴	Resveratrol, genistein or both	<i>In vivo</i> SV40 large T-antigen-targeted probasin promoter rat model	Genistein and resveratrol treatment alone or in high-dose combinations suppressed prostate cancer development; Treatment with both polyphenols decreased cell proliferation and IGF-1 protein expression; Genistein alone induced apoptosis and decreased NCoA-3 in ventral prostate	Inhibition of cell proliferation, IGF-1 expression and upregulation of AR by resveratrol; Induction of apoptosis and inhibition of NCoA-3 signalling by genistein
Narayanan <i>et al.</i> (2009) ¹²⁹	Resveratrol and curcumin (with or without liposomal encapsulation)	<i>In vitro</i> PTEN-CaP8; <i>In vivo</i> prostate-specific PTEN knockout mouse model	Combination of liposomal forms of curcumin and resveratrol decreased prostatic adenocarcinoma <i>in vivo</i> , inhibited cell growth and induced apoptosis <i>in vitro</i>	Downregulation of targets (p-AKT, cyclin D1, mTOR and AR) that are activated by <i>PTEN</i> loss
Wang <i>et al.</i> (2008) ¹²⁶	Resveratrol alone	<i>In vitro</i> LNCaP; <i>In vivo</i> LNCaP xenografts in athymic Balb/c and AnNCr-nu/nu nude mice	Inhibited cell growth; Delayed initial development of LNCaP tumours; Resveratrol exposure promoted angiogenesis and inhibition of apoptosis in LNCaP xenograft model	Modulation of steroid hormone-dependent pathways (androgen-mediated and oestrogen-mediated events) [‡]
Seeni <i>et al.</i> (2008) ¹²²	Resveratrol alone	<i>In vivo</i> TRAP model	Suppression of prostate cancer growth and induction of apoptosis without toxicity	Downregulation of AR expression; Suppression of the androgen response to glandular kallikrein 11 [§]

^{*} Preliminary data suggest that resveratrol might be harmful; caution is advised when using resveratrol in human patients until further studies are conducted.

[‡] *In vivo* exposure is a concern due to increased angiogenesis and inhibited apoptosis.

[§] Provides mechanistic basis for resveratrol chemopreventive efficacy against prostate cancer.

Abbreviations: AR, androgen receptor; IGF-1, insulin-like growth factor-1; IGFBP-2, insulin-like growth factor binding protein 2; mTOR, mammalian target of rapamycin; NA, not applicable; NCoA-3, Nuclear receptor coactivator 3 (also known as steroid receptor coactivator protein 3); PSA, prostate-specific antigen; SCID, severe combined immunodeficiency; TRAIL, TNF-related apoptosis-inducing ligand; TRAMP, transgenic adenocarcinoma of mouse prostate; TRAP, transgenic rat for adenocarcinoma of prostate.

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