Prostate cancer is the most common malignancy in men and the second leading cause of death from cancer in Western society. Due to the introduction of prostate-specific antigen screening, insignificant tumors are being over-diagnosed and patients who may not benefit from curative procedures (i.e., surgery or radiotherapy) are being overtreated, and resultantly may suffer the consequences of these procedures, leading to decreased quality of life. Thus, prostate cancer prevention could result in saving lives and, even if this goal cannot be achieved, reduction of morbidity and economic gains are significant end points that may be reached. Many compounds have been hypothesized as possible chemoprevention agents in epidemiological or observational studies. However, there are few clinical trials available in the current literature. This article reviews the main clinical trials that have been published regarding prostate cancer chemoprevention.

Pharmacological intervention is discussed through papers suggesting that 5α-reductase inhibitors, such as dutasteride and finasteride, may prevent prostate cancer. Toremifene and statins are also possible chemoprevention agents. Dietary supplementation with selenium, vitamins A, C, D and E, folic acid, green tea, soy and lycopene are also debated.

**Keywords:** 5α-reductase inhibitor • selective estrogen-receptor modulators • selenium • vitamin E (α-tocopherol)

Prostate cancer (PCa) is the second most common malignancy in the western world and the second leading cause of death among all cancers. Age, ethnicity and family history are the most important risk factors for the development of PCa, but suffice to say, are not modifiable. Although overall the quality of the studies is poor (e.g., ecological and case-control), there is a huge body of evidence suggesting that environmental factors and diet play an important role in PCa carcinogenesis and development. Due to its high incidence and modifiable risk factors [1], PCa may be a preventable disease.

Since the implementation of prostate-specific antigen (PSA) testing in clinical practice, the number of men diagnosed and treated for early-stage disease has dramatically increased. The large discrepancy between histological incidence of and mortality from, PCa has outlined the risks of over-detection (and often overtreatment) of some PCas that would not have put patients’ life at risk. It has become fairly clear for many people involved in PCa management that preventing the diagnosis of so-called ‘clinically insignificant lesions’ may drastically reduce PCa overtreatment and its eventual negative effect on patient quality of life.

Active surveillance (AS) is an increasing treatment option for patients with indolent localized PCa tumors [2]. However, even in these patients who are potential candidates for AS, for various reasons, curative procedures with intent-to-treat are still the most used approaches. Thus, as a consequence, a reduction in the number...
of biologically indolent tumors diagnosed would yield huge public health benefits, such as reduced costs related to surgery/radiation therapy or AS follow-up protocols. In addition, patients could avoid the psychological burden of living with the diagnosis of cancer and its related quality of life issues.

Regarding chemoprevention, for most considerable risk factors and potential targets, we are unfortunately lacking high quality evidence. With regards to modifiable PCa risk factors, most studies deal with in vitro or in vivo animal models, or are observational epidemiologic studies. In the current era of evidence-based medicine, few randomized clinical trials are available to support the use of drugs or nutritional supplements as chemopreventive agents for PCa.

In this review, we will focus on interventions tested in clinical trials as primary prevention for PCa, discuss how modifiable risk factors can be managed and prevention strategies implemented in clinical practice. Studies were identified by a search of the PubMed database through to the end of June 2011. In the absence of clinical trials, we opted to cite the best evidence available and discuss its results.

Hormonal agents

■ 5a-reductase inhibitors

Primary chemoprevention

Interventions that alter circulating androgen levels or inhibit 5a-reductase have potential as chemopreventive agents because testosterone, after conversion to 5a-dihydrotestosterone, among many other mechanisms controls prostate mitotic activity and potentially cancer development. There are two 5α-reductase inhibitors (5α-RIs): finasteride, which is selective for the type 2 isoenzyme (5α-R2), and dutasteride, which inhibits both type 1 (5α-R1) and type 2 (5α-R2) isoenzymes.

Finasteride

The Prostate Cancer Prevention Trial (PCPT) [3] was the first prospective clinical trial dealing with PCa chemoprevention that showed a positive result, namely the ability of a compound to significantly reduce PCa diagnosis in treated patients compared with placebo.

During this 7 year study, 18,882 men, without a baseline biopsy, 55 years of age or older with a normal digital rectal examination (DRE) and a PSA level of 3.0 ng/ml or lower were randomly assigned to treatment with finasteride 5 mg/day. On follow-up, sextant prostate biopsy was recommended ‘for-cause’ if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/ml or if the DRE was abnormal. An end-of-study sextant prostate biopsy was also performed.

The PCa prevalence was 24.4% in the placebo group and 18.4% in the finasteride group, accounting for a 24.8% reduction in the risk of being diagnosed with PCa at 7 years, despite the fact that the absolute benefit was less impressive among cancers detected by for-cause biopsies. However, intermediate- or high-risk PCas, according to Gleason histologic grade stratification, were significantly more common in the finasteride group (37% of the diagnosed tumors) than in the placebo group (22.2% of the diagnosed tumors). Libido decrease and erectile dysfunction (6%) were more frequent in the finasteride group as well as a small number of mastodynia and gynecomastia related to the use of 5α-RI. However, urinary complaints were improved in men assigned to receive finasteride.

Many explanations have been brought up to explain the increase in high-grade disease observed in individuals treated with finasteride during the PCPT trial. One possibility was that this observed incidence was a true phenomenon. Finasteride could actually cause grade progression by inducing some genetic instability leading to a more aggressive phenotype [4].

However, many papers and authors have disputed that the increased number of high-grade disease in the finasteride arm was a true phenomenon, but rather could be hypothetically explained either by pathological interpretation artifacts, artifacts secondary to PSA adjustment or volume-grade artifact.

Although pathological architectural changes toward higher Gleason grades are frequently observed in patients under hormonal therapy, and in men receiving finasteride [5], there is now a consensus that the increased number of high-grade disease was not related to pathological artifacts.

Considering artifacts secondary to PSA adjustment, PSA values in the finasteride group were calculated through a multiplier in order to compensate for the expected reduction in its serum levels caused by the drug (~50%). In fact, the sensitivity of an elevated PSA level for the detection of PCa, including high-grade tumors, was increased in the finasteride group of the PCPT. One explanation is that subjects harboring high Gleason cancers could have had lower PSA reductions and therefore more for-cause biopsies would have been requested. The question that remains is why this eventual bias was not unmasked by the end-of-study biopsy. The observation that the increased risk of high-grade tumors persisted in analyses of scheduled biopsies independent of PSA results argues against PSA-related detection bias as the cause of the observed increase in the incidence of high-grade tumors.

The volume-grade artifact was increasingly accepted as a plausible reason since finasteride shrinks the prostate gland volume by approximately 20%, and, in men
with smaller prostates, foci of pre-existing high-grade lesions have a higher probability of being biopsied [6], since an increased sampling density occurs. In fact, the rates of more aggressive disease were not in concordance with the biopsy results among subjects who underwent radical treatment [7], with a higher number of patients in the placebo arm (8.2%) than in the finasteride arm (6.0%) being found to have high-grade disease equivalent to a relative risk reduction of 27% in favor of finasteride [8]. However, recently the US FDA repeated the same analyses [9], statistically adjusting for prostate volume and using a modified Gleason score of 8–10 as the definition of a high-grade tumor, instead of the original definition of score 7–10 used at the first analysis. The results did not support the contention that increased sampling density is responsible for the increased incidence of high-grade tumors in the finasteride group.

One question that remains is whether the PCPT trial was a real prevention trial or whether it simply prevented the detection of some PCa because many of the low-grade tumors were ‘washed out’ by finasteride and not amenable to diagnosis by the pathologist.

Dutasteride
Dutasteride is another 5α-R1 that has been used in the treatment of symptomatic benign prostatic hyperplasia (BPH). Like finasteride, dutasteride inhibits the 5α-R2, but unlike finasteride, it also inhibits the 5α-R1. The role of this type I receptor in prostatic carcinogenesis continues to be defined. The 5α-R1 expression seems to be increased in PCa and this expression increases as one migrates along the spectrum of more advanced disease. Studies have shown that, similar to protein levels, 5α-R1 mRNA levels are increased in PCa. In particular, 5α-R1 mRNA expression is significantly increased in PCa compared with normal and BPH tissue. In contrast, several studies have shown decreased expression of 5α-R2 in localized PCa compared with normal/BPH tissue [10].

Benefiting from the PCPT experience, the REDUCE trial [11] was designed as a 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study where dutasteride (0.5 mg daily) was compared with placebo.

To start, the study aimed at a higher risk population [12], accruing men ≥50 years of age with serum PSA levels between 2.5 and 10.0 ng/ml. Furthermore, REDUCE inclusion criteria included a negative 6–12 core prostate biopsy, without the presence of HGPIN or atypical small acinar proliferation (ASAP) within 6 months of the beginning of the trial. Therefore, limited for-cause biopsies were expected. Instead, ten core biopsies at 2 and 4 years were added in the protocol. There was a benefit effect in reducing the rate of acute urinary retention, but adverse events as in PCPT, such as libido and erectile dysfunction, were encountered more frequently in the dutasteride group than in the placebo group.

The trial results observed in 6729 men were consistent with a relative risk reduction in the number of PCa cases of 22.8% in favor of dutasteride, which is similar to what was found in PCPT. However, the main outcome difference between the two trials was that dutasteride did not significantly affect the diagnosis of Gleason grade 7–10 PCa, in contrast with PCPT.

However, a recent presentation reassessed biopsy specimens according to the modified Gleason scale, by an independent pathologist who was unaware of the earlier scores [10]. This analysis was not originally reported in the REDUCE trial. No reduction in the incidence of tumors with modified Gleason scores between 7 and 10 was observed, a finding that is consistent with the published data. However, if we take into consideration the most accepted concept of high-risk disease, an absolute increase of 0.5% in the incidence of tumors with modified Gleason scores of 8 to 10 (relative risk: 2.06) was seen with dutasteride treatment. This increase is similar to the absolute increase of 0.7% in the incidence of such tumors observed with finasteride treatment (relative risk: 1.70). These results suggest that one additional man would receive a diagnosis of high-grade PCa for every 150–200 men treated long term with a 5α-R1. Thus, the evidence is insufficient to claim superiority of dutasteride over finasteride, because the two study populations and follow-up protocols are profoundly different [13].

The CombAT study [14], which was designed to evaluate men with BPH, has shown that dutasteride, alone or in combination with tamsulosin, significantly reduces the relative risk of PCa diagnosis in men with BPH undergoing annual DRE and PSA screening. During this 4-year, randomized, double-blind, parallel-group study with 4844 men ≥50 years of age with clinically diagnosed moderate-to-severe BPH and baselines International Prostate Symptom Score ≥12, prostate volume ≥30 ml, and serum PSA 1.5–10 ng/ml, prostate biopsy was performed for-cause (clinical suspicion because of symptoms, abnormal DRE, or abnormal PSA level); or at the end of the study, in the setting of a PSA level of >4 ng/ml and/or suspicious DRE.

The results indicated that dutasteride (alone or in combination with tamsulosin) was associated with a 40% relative risk reduction of PCa diagnosis compared with tamsulosin monotherapy (combination therapy absolute risk of PCa: 2.3%; dutasteride monotherapy absolute risk of PCa: 2.6%; and tamsulosin absolute risk of PCa: 3.9%) and a 40% reduction in the likelihood of
biopsy, thus, men taking 5α-RIs underwent fewer procedures. Those reductions were similar both in low- and high-grade Gleason score cancers, maybe due to lack of power. Furthermore, biopsy rate in the group receiving dutasteride trended toward a higher diagnostic yield (chances of cancer detection on PSA-driven biopsies were 29, 28 and 24%, respectively, for combination therapy, dutasteride and tamsulosin groups).

These findings suggest that dutasteride may play an important role in daily clinical practice, once it drives biopsy with a higher diagnostic yield through PSA performance improvement, reducing the percentage of an unnecessary potentially risky procedure that is associated with increased complication rates in recent years [15].

Andriole et al. analyzing the REDUCE population, evaluated if dutasteride enhanced the usefulness of total PSA for diagnosing clinically significant PCa [16]. They found that the degree of PSA increase after 6 months was a better indicator of clinically significant cancer in the dutasteride arm than in the placebo arm. Conversely, the initial decrease in PSA in men taking dutasteride did not predict the likelihood of PCa.

In March 2011, GlaxoSmithKline (GSK) announced that they will no longer pursue global approval for the use of Avodart™ (dutasteride) to reduce the risk of PCa. GSK have withdrawn applications from regulatory review where procedures are ongoing and, in the limited number of countries where dutasteride is already indicated for use in PCa risk reduction, GSK will work with regulatory agencies to remove this indication from the product’s license and support physicians to communicate appropriately to patients. This withdrawal was based on the Complete Response letter following an FDA Oncologic Drugs Advisory Committee Meeting in December 2010, where the majority voted against a favorable risk–benefit profile for dutasteride for reduction in the risk of PCa in men at risk for the disease. This decision was essentially due to questions regarding the clinical significance of reducing the risk of low-grade PCa, and uncertainties surrounding the possible explanations for the increased number of cases of high-grade tumors in men treated with 5α-RIs for PCa risk reduction. GSK also received similar feedback from Sweden, the Reference Member State in Europe and has now notified the Swedish Medical Products Agency of its withdrawal from the regulatory review.

Overall, a combination of factors including the ongoing medical and scientific debate around the benefits and risks of 5α-RIs for PCa risk reduction, together with feedback from regulatory agencies, has caused GSK to carefully consider its approach to the indication and subsequently withdraw ongoing applications for approval.

Summary of the role of 5α-RIs for PCa chemoprevention

A recent Cochrane review estimated the benefits and harms of 5α-RIs in preventing PCa [17]. Eight prospective randomized clinical trials, including 41,638 men, were scrutinized. Study duration ranged from 1–7 years, with four trials enrolling a total of 34,997 (84%) men lasting ≥4 years. Five studies assessed the effect of 5α-RIs on BPH and only the PCPT and the REDUCE trials focused on the impact of 5α-RIs on PCa period prevalence as a primary end point.

Overall, the subject mean age was 64 years, enrollees were mostly Caucasian (92%), the mean baseline PSA level was 3.1 ng/ml and mean prostate volume was 51.2 ml.

Compared with placebo, 5α-RIs resulted in a 25% relative risk reduction in PCas detected for-cause, with an absolute risk reduction from 4.9 to 3.5%. There were reductions across age, family history of PCa, PSA level and prostate volume subgroups. However, it confirmed that the incidence of erectile dysfunction, decreased ejaculate volume, decreased libido and gynaecomastia were greater in the 5α-RI group when compared with placebo.

On the other hand, the trade-off inherent in using a 5α-RI for PCa prevention is the acceptance of one additional high-grade cancer in order to avert three to four potentially clinically relevant lower grade cancers. The conclusion drawn by the advisory committee in December 2010 was that finasteride and dutasteride did not have a favorable risk–benefit profile for the proposed use of chemoprevention of PCa in healthy men [9].

Cost–effectiveness analysis

The economic impact of pharmacological chemoprevention strategies has been analyzed in different ways. Although there are no definitive data supporting that finasteride reduces PCa mortality, Unger et al. published an analysis of the PCPT results on a population-wide level [18]. In their analysis, even with the assumption that the high-grade cancer findings were true, over 260,000 life-years would be saved per year in the USA since the potential detrimental effects of an increased rate of patients with high-grade Gleason scores (every increase of 5% in the proportion of high-grade tumors in the general cancer population due to finasteride reduces person-years saved by approximately 30,000) would be outweighed by a reduction in incidence.

The cost utility of chemoprevention using dutasteride has also been evaluated. It is unlikely to be cost effective when considering the impact on survival differences among treated versus untreated groups in the general population owing to the high costs of the
significant differences were that men who took a 5α-RI at baseline. After a median follow-up of 38.5 months, 
drug and multiple years of treatment required before 
gains are realized [19]. Dutasteride chemoprevention is 
associated with a gain of 108 quality-adjusted life-
years (QALY) per 1000 men and the quality-adjusted 
cost–effectiveness ratio for dutasteride compared with 
men not receiving chemoprevention was US$140,240 
per QALY. At a cost of $626 per year, a cost benefit
from dutasteride with a willingness-to-pay threshold 
lower than $50K was predicted. Assuming a 15% period 
prevalence renders an incremental cost–effectiveness 
ration of $576,630 per QALY and a 30% period prevalence 
would yield $98,059 per QALY. In conclusion, 
chemoprevention may be cost effective and represents 
good value for money in high-risk populations when 
taking into consideration adjustments for the impact on 
quality of life [20].

Secondary prevention: use of 5α-RI in the active 
surveillance setting

The idea of secondary prevention is particularly appealing in 
PCa in men followed by AS. AS refers to deferring treatment in 
many men with low risk disease who are unlikely to die from it if left untreated and treating them 
only if they demonstrate signs of disease progression.

Clinicians currently perform many biopsies in 
patients undergoing AS as there is no accurate test 
to detect aggressive PCa or to predict those patients 
who are at risk of progressing during AS. Secondary 
chemoprevention could reduce the number of men with 
low-grade tumors requiring treatment, decrease 
patient anxiety if repeat biopsies prove negative as well as reducing adverse events from surgical treatment.

Although analyzed retrospectively, 5α-RIIs have been 
studied in patients with a confirmed diagnosis of PCa 
undergoing AS with small volume disease in Toronto (University Health Network, Canada) [21]. Clinical 
and pathologic variables for men taking a 5α-RI were 
similar to those who did not. Notably, the only significant differences were that men who took a 5α-RI had a larger median prostate size (61 vs 41 ml) and significantly higher PSA (5.4 vs 4.8 ng/ml) at diagnosis; therefore, the groups can be considered similar at baseline. After a median follow-up of 38.5 months, 
32% of the patients experienced pathologic progression (defined as Gleason score >6, maximum core involvement >50%, or more than three cores positive on a follow-up prostate biopsy) and 33% abandoned AS. Men taking a 5α-RI experienced a lower rate of pathologic progression (18.6 vs 36.7) and were less likely to abandon AS (20% vs 37.6%). This retrospective study, which included patients treated both with finasteride and dutasteride, supported the data of a well-designed prospective randomized study presented by Fleschner et al. [22].

The REDEEM study tested whether dutasteride controlled growth of existing low-risk, localized PCAs and, hence, reduced the need for aggressive therapy in men followed with AS [23]. More than 300 men, aged 48–82 years, with PSA <11 ng/ml and Gleason score ≤6 PCa (≤3 cores positive, <50% of any core positive) were randomized to dutasteride or placebo for 3 years. Repeat 12-core biopsies were performed at 18 and 36 months, or for-cause at other times during the study. The primary end point was time-to-progression, defined as the earliest of either pathological progression (Gleason score >6, ≥4 cores positive or >50% of any core positive) or therapeutic progression (radical prostatectomy, radiation therapy or hormonal ablation). Dutasteride reduced time to PCa progression (relative risk reduction 38.9% p = 0.007). 23% of men (n = 31) in the placebo group and 36% of men (n = 50) in the dutasteride group had no cancer detected on their final biopsy. PCa-related anxiety was reduced in the dutasteride arm compared with the placebo arm (p = 0.036), based on the Memorial Anxiety Scale for PCa. Drug-related adverse events were similar to those previously reported for dutasteride. In this randomized study including men followed with AS, dutasteride delayed the time to PCa progression, increased the percentage of men with no detectable PCa, and improved PCa-related anxiety. There was no evidence of increased Gleason score upgrading with dutasteride.

Selective estrogen-receptor modifiers

Estrogen-receptor modulation by selective estrogen-receptor modifiers (SERMs) such as toremifene has been tested in animal models to prevent PCa with positive results [24]. In a Phase IIb trial [25] with 514 men with HGPIN, toremifene 20 mg/day had better results when compared with higher doses (40 and 60 mg/day) and placebo, with a cumulative risk reduction at 12 months of 48.2% versus placebo (absolute PCa incidence at 12 months: toremifene 20 mg = 9.1%, toremifene 40 mg = 14.3%, toremifene 60 mg = 13% and placebo = 17.4%). There were no Gleason or prostate volume differences among groups and the side effects were comparable. Results of a completed Phase III trial comparing toremifene 20 mg and placebo are expected [102].

Statins

There is strong epidemiologic evidence linking dietary 
fat and PCa. This article will not focus on this topic due to the absence of clinical trials.

Statins or cholesterol-lowering drugs or heart healthy agents are an ideal choice for a large chemoprevention trial for numerous reasons, including:
Cardiovascular disease (CVD) has been the number one cause of death in men and women every year in the USA since 1900; CVD has been the number one cause of death in the major cancer chemoprevention trials; CVD has been the number one or two cause of death of men and women post diagnosis of breast cancer, colorectal cancer and PCa.

A large case-control study by Graaf et al. analyzed data from approximately 300,000 residents of eight Dutch cities [26]. The mean follow-up period was approximately 7 years. Individuals receiving statin prescriptions for a minimum of 6 months were primarily prescribed simvastatin, but other prescribed statins included pravastatin, fluvastatin, atorvastatin or a combination (10.9%). A total of 3129 cancer cases were located and matched to 16,976 control subjects. The use of statin drugs was associated with a 20% reduction in the risk for cancer (OR = 0.80). Statins also were associated with a 36% reduction in cancer risk when taken for longer than 4 years (OR = 0.64). There was a 63% reduction in PCa.

On the other hand, the REDUCE trial participants were divided according to statin intake [27]. Among men who underwent at least one on-study biopsy (n = 6729), the association between baseline statin use and risk of high-grade (Gleason ≥7) versus no cancer was examined using multimonial logistic regression adjusting for age, race, baseline PSA, prostate volume, rectal examination findings and BMI. Overall, 1174 men were on a statin at baseline. They were older, had lower PSA levels, higher BMI values, and lower serum testosterone and dihydrotestosterone levels. The results showed that statin use was not associated with low- (relative risk ratio: 1.05) or high-grade cancer (relative risk ratio: 1.14) risk on multivariate analysis.

Thus, due to contradictory data, clinical trials of statins for PCa prevention are warranted.

Nutritional supplements

Selenium & vitamins A, C & E

In 1996 the Nutritional Prevention of Cancer (NPC) trial was published [28]. It was a multicenter, double-blinded, randomized, placebo-controlled cancer prevention trial undertaken to examine the role of selenium in preventing skin cancer. A total of 1312 patients (mean age: 63 years) with a history of basal cell or squamous cell carcinomas of the skin were randomized from 1983 through 1991. Patients were divided into two groups and treated with oral administration of selenium 200 µg/day or placebo for a mean of 4.5 years and had a total follow-up of 6.4 years. Even though it did not decrease skin cancer incidence, analysis of secondary end points revealed that compared with controls, patients taking selenium had a non-significant reduction in all-cause mortality and a significant reduction in other forms of cancer, as well as in cancer mortality. For instance, PCa was reduced by a stunning 63%.

Approximately 2 years later, the role of vitamins E and A in PCa chemoprevention was analyzed in the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study [29], which was designed to assess lung cancer as the primary end point. A total of 29,133 male smokers between 50 and 70 years of age from Finland were randomly assigned to receive α-tocopherol (50 mg), β-carotene (20 mg), both agents, or placebo daily for a median of 6.1 years. Although among subjects receiving β-carotene, PCa incidence and mortality were 23 and 15% higher compared with those not receiving it, respectively, and individuals who were administered vitamin E had better outcomes. A 32% decrease in the incidence of PCa was observed, along with an evident reduction in clinical PCa, but not in latent cancer. Furthermore, mortality from PCa was 41% lower among men receiving α-tocopherol.

These findings, combined with animal data supporting the rationale of using these compounds for PCa prevention, were responsible for the impetus of developing a larger randomized study combining selenium and vitamin E.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) studied the role of selenium and vitamin E for preventing PCa in North and Central American countries, such as Canada, the USA and Puerto Rico [30]. The study was designed as a Phase III, prospective, multicentric, randomized trial with four distinct approximately equal groups. Between 2001 and 2004, 35,533 healthy men received selenium 200 µg/day, in the form of pure l-selenomethionine, or 400 IU of vitamin E in the form of synthetic rac-α-tocopherol acetate, or a combination of both, or placebo. The baseline ages of males selected were 50 years or older for African–Americans, and 5 years or older for all others. All men had a serum PSA level of 4 ng/ml or less, and a DRE not suspicious for PCa.

No significant differences in PCa incidence were observed in any of the groups (absolute risk data: placebo = 4.43%; selenium = 4.56%; vitamin E = 4.93%; and selenium + vitamin E = 4.56%). At a median follow-up of 5.46 years, hazard ratios for PCa were 1.13 for vitamin E, 1.04 for selenium and 1.05 for selenium associated with vitamin E versus 1.00 for placebo. Thus, slight but statistically non-significant increases
were observed in PCa risk within treated groups. In addition, there was a higher risk of Type 2 diabetes mellitus within the selenium group (relative risk = 1.07). Therefore, although SELECT was planned to include a 12-year intervention period, the interim analysis in 2008 recommended the discontinuation of the study due to the negative results and no evidence of benefit from either agent [34].

Taking into consideration differences and similarities between SELECT and the earlier clinical trials and trying to understand why there were discrepant results, one may observe that SELECT used pure l-selenomethionine as the intervention agent, whereas other human trials and animal studies have demonstrated anti-tumorigenic efficacy for selenite and selenium-enriched baker’s yeast [32]. Selenomethionine differs from the other selenium compounds because these are methylated to form methylselenol, a presumptive anti-tumorigenic metabolite. In a mouse model, it has been proven that monomethylated selenium is more efficient in cancer prevention than other selenium compounds, thus emphasizing the role of small molecular weight selenocompounds in cancer prevention [33].

One other striking difference was the selenium plasma levels in individuals enrolled in the NPC trial and in the SELECT trial. Subjects in SELECT had higher initial plasma levels of selenium than those in the NPC trial (135 and 113 ng/ml, respectively). In addition, retrospective re-analyses showed that the treatment effect in the NPC trial was restricted to those with lower baseline plasma selenium concentrations, with this subgroup benefiting by selenium supplementation in reducing cancer risks [34].

Regarding vitamin E, the high dose (400 IU/day) of the α-tocopherol form of vitamin E in SELECT may have been less effective than an eightfold lower dose of 50 mg/day (roughly equivalent to 50 IU/day) used in the ATBC study. Higher pharmacological doses of α-tocopherol may have an adverse effect on cytochrome p450 enzyme and other regulatory mechanisms that a lower dose would not have [35]. Plasma or tissue levels of α-tocopherol within the physiological range, such as through a 50 mg/day supplement, may have some cancer preventive effect such as cell proliferation or tumor growth inhibition [36] that may not be seen with supra-physiological doses of vitamin E.

Other facts that need to be taken into account are that there is a potential for contamination of the placebo group, given that the active treatments are available without prescription. In addition, both NPC and ATBC studies had PCa as a secondary end point. Thus, investigators did not systematically identify prevalent or incident cancers, and these cancers were more likely to be clinically detected, as opposed to SELECT where PSA-detection was more likely. The chance that at least one of the not primarily analyzed cancer types would be reduced is substantial (type 2 error).

Another negative, randomized, double-blind, placebo-controlled trial assessing vitamins and PCa was published in 2009. The Physicians’ Health Study II was designed to evaluate whether long-term vitamin E or C supplementation decreased the risk of PCa [37]. It began in 1997 and continued until its completion 10 years later and included 14,641 men 50 years or older that received supplementation of 400 IU of vitamin E every other day and 500 mg of vitamin C daily. No effect of vitamin E was found on PCa incidence (hazard ratio = 0.97). There was also no significant effect of vitamin C on PCa incidence (hazard ratio = 1.02).

Finally, very recently, the results of another negative, randomized, Phase III, double-blind study of daily soy (40 g), vitamin E (800 IU) and selenium (200 µg) versus placebo in men with HGPIN were reported by Fleshner et al. [38]. A total of 303 men in 12 Canadian centers were analyzed. The main eligibility criterion was confirmed HGPIN in at least one of two biopsies within 18 months of random assignment. Treatment was administered daily for 3 years. Follow-up prostate biopsies occurred at 6, 12, 24 and 36 months post-randomization. Invasive PCa developed equally in both groups, being diagnosed in 26.4% of all patients. This trial did not support the hypothesis that combination of vitamin E, selenium and soy prevents progression from HGPIN to PCa.

**Aspirin & folic acid**

A recently published study assessed deaths due to cancer during and after randomized trials of daily aspirin versus control, conducted originally for prevention of vascular events [39]. Subjects under medication presented some benefit only after 5 years’ follow-up. The 20-year risk of cancer death remained lower in the aspirin groups than in the control groups and benefit increased with scheduled duration of trial treatment.

The Aspirin/Folate Polyp Prevention Study was a placebo-controlled, randomized trial of aspirin and folic acid supplementation for the chemoprevention of colorectal adenomas conducted between 1994 and 2006, and participants were followed for a median of 7 years [40]. Results showed that aspirin alone had no statistically significant effect on PCa incidence, but there were marked differences based on folic acid treatment. The estimated probability of being diagnosed with PCa over a 10-year period was 9.7% in the folic acid group and 3.3% in the placebo group (age-adjusted...
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hazard ratio = 2.63), which is statistically significant. In contrast, baseline dietary folate intake and plasma folate in non-multivitamin users were inversely associated with risk of PCa, although these associations did not attain statistical significance. The reason for the contrasting associations of folate supplementation and baseline intake or circulating levels of folate with the risk of PCa is unknown.

Folate supplementation was in the form of folic acid, a fully oxidized, monoglutamyl form of folate that may differ in its effects from the natural reduced and methylated forms. Another debatable hypothesis is that dietary folate could be associated with some other, not analyzed nutrient that caused a spurious association between folate and reduced PCa. Thus, the role of folate in PCa is quite complex. Furthermore, given the low occurrence of PCa in this study, the estimate of PCa risk in the placebo and folic acid groups should be interpreted with caution.

- **Lycopene & tomato products**

There are no clinical trials analyzing tomato products, lycopene (α-carotenoïd from tomatoes) and PCa risk. Overall, however, the data are inconclusive. Some studies suggest that frequent intake of these substances is associated with a reduced risk of PCa while others could not replicate this result.

In the Health Professionals Follow-Up Study (HPFS), between 1986 and 1998, 2481 cases of PCa were diagnosed among 47,365 men who completed dietary questionnaires [41]. The results confirmed that lycopene intake was associated with a reduced risk of PCa (risk relative for high versus low quintiles = 0.84); intake of tomato sauce, the primary source of bioavailable lycopene, was associated with an even greater reduction in PCa risk (risk relative for 2+ servings/week vs <1 serving/month = 0.77), especially for locally advanced cancers. However, in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), where participants completed a 137-item food frequency questionnaire at baseline and were followed for 4.2 years, lycopene/tomato product consumption did not protect from PCa [42]. In the 1338 cases of PCa identified among 29,361 men, lycopene intake and tomato-based foods were not associated with PCa risk. However, among men with a family history of PCa, risks were decreased in relation to increased consumption of lycopene and specific tomato-based foods.

- **Green tea**

The administration of green tea catechin (GTC) might be beneficial during the carcinogenic process. Contradictory observational publications evaluating the same population group have shown that, on one hand, consumption was associated with a dose-dependent decrease in the risk of advanced PCa (multivariate relative risk of 0.52 for men drinking five or more cups/day compared with <1 cup/day) [43]. However, on the other hand, this statistical significant relative risk reduction was not achieved by others [44].

In a clinical trial with 60 volunteers diagnosed with high HGPIN [45], men consumed GTCs (600 mg/day, three-times a day) or placebo for 1 year and received two follow-up saturation biopsies at 6 months and 1 year. The incidence of PCa was 3% in the GTCs-arm and 30% in the placebo-arm. Another round of prostate mapping was performed in nine patients from the placebo-arm and 13 from the GTCs-arm, with mean follow-up from the end of GTCs dosing of 23.3 and 19.1 months, respectively. Three other cases of cancer appeared during follow-up, two in the placebo arm and one in the GTCs-arm, leading to an almost 80% reduction in PCa diagnosis, and suggesting that the inhibition of PCa progression achieved in these subjects was long-lasting [46]. No other studies have confirmed these data.

- **Soy**

Since isoflavones induce cell cycle arrest, avoid tumor proliferation in tumor model systems and may influence the α-estrogen receptor, linked to prostate carcinogenesis [47], a Phase III Canadian trial among men with HGPIN has been designed and completed. The negative results have been reported in the previous section about vitamin E and selenium [38].

**Future perspective**

Improved understanding of the biologic pathways that lead to PCa is a sound approach to develop chemoprevention strategies. Association and possibly cumulative effect of different drugs shown to reduce the risk of PCa by themselves, such 5α-RIs and SERMs, could be an interesting route to be pursued.

The molecular effects of finasteride, in combination with dietary soy supplementation, in patients at high risk for the development of PCa is being studied [102].

The IGF-1 is considered to be an alternative pathway for PCa growth. Ongoing clinical trials to confirm metformin antineoplastic activity on PCa are needed as the evidence currently available for standard practice is lacking.

We should improve our understanding of selenium and prostate biology. Despite the understandable disappointment of the SELECT trial, one could consider not completely abandoning this route. On one hand, selenium-containing proteins, such as thioredoxin reductase 1, may prevent cancer, but once the malignancy is initiated thioredoxin reductase 1 may
Actually contribute to progression of the disease\cite{48}. On the other hand, selenium deficiency may protect against tumorigenesis development in some mouse cancer models\cite{49}. As a result, in the future, selenium supplementation may be targeted to a subset of the human population, or even to individuals of a certain genotype, disease state or selenium status, that can benefit most from this micronutrient. Subanalyses of the SELECT trial should investigate whether some subgroups of men responded differently than the overall population. A randomized Phase III trial with different doses of high-selenium baker’s yeast supplementation\cite{104} will start recruiting soon and may help to understand the true role of selenium in PCa chemoprevention.

Uncertainty remains about the possible association of lycopene and tomato product intake and risk of PCa. Antioxidant properties have been hypothesized to be primarily responsible for their beneficial effects and recent studies suggests that other mechanisms mediated by steroid hormones, with testosterone decrease and estradiol increase, may also be involved\cite{50}. A multicenter, prospective, randomized, double-blinded, placebo-controlled trial may be performed to clarify the real role of those substances as nutritional supplements in reducing PCa incidence.

We expect the results of a large trial currently underway to better assess the precise role of green tea catechin in the chemoprevention approach of patients at higher risk of PCa\cite{105}.

Thus, this theme will evolve dramatically in the next 5–10 years and the results of current ongoing trials may change dramatically the way we deal with PCa, not only because of deaths that will be prevented but, we believe, mainly because of the reduction of overtreatment and its consequences.

### Executive summary

- The PCPT trial demonstrated that finasteride is associated with 24.8% reduction in the risk of being diagnosed with prostate cancer (PCa) at 7 years.
- According to Gleason histologic grade stratification, intermediate- or high-risk PCas were significantly more common in the finasteride group.
- The increase of high risk tumors in the finasteride group could at least partially be caused by detection bias, but to what extent this explains the increase is uncertain.
- REDUCE trial demonstrated that dutasteride is associated with 22.8% reduction in the risk of being diagnosed with PCa.
- Dutasteride did not significantly affect the diagnosis of Gleason 7–10 PCa.
- CombAT trial demonstrated that dutasteride is associated with a 40% reduction in the likelihood of biopsy and that it has higher diagnostic yield.
- Dutasteride is not approved for the prevention of PCa. In June 2011, the FDA notified healthcare professionals that the Warnings and Precautions section of the labels for the 5α-reductase inhibitor (5α-Ri) class of drugs has been revised to include new safety information about the increased risk of being diagnosed with a more serious form of PCa (high-grade PCa). GSK has subsequently withdrawn applications to market dutasteride for PCa risk reduction.
- Patients with PCa receiving dutasteride and enrolled in an AS protocol may have a delayed time to disease progression and reduced PCa-related anxiety.
- Low dose of toremifene was associated with reduced PCa detection in a Phase IIb study of patients with HGPIN.
- If used for long periods of time, statins may be associated with PCa risk reduction.
- Clinical trials are needed.
- Initial data suggested that selenium and vitamin E supplementation were associated with PCa chemoprevention. In the NPC trial selenium (200 mg/day) was associated with 63% reduction in the risk of being diagnosed with PCa and in the ATBC trial vitamin E (α-tocopherol 50 mg/day) was associated with 32% reduction in the risk of being diagnosed with PCa.
- SELECT trial was discontinued because neither selenium (200 μg l-selenomethionine/day), vitamin E (400 IU of synthetic rac-α-tocopherol acetate/day) nor the intake of both was associated with PCa risk reduction.
- A randomized trial in men with HGPIN failed to demonstrate that vitamin E, selenium and soy prevented progression from HGPIN to PCa.
- Differences in the form of selenium administration and vitamin E dose may explain the different results.
- Selenium seems to play a more important role in individuals with low selenium plasma levels.
- Phase II trial demonstrated that vitamin C and supplementation is not associated with PCa risk reduction.
- ATBC trial demonstrated that vitamin A (β-carotene) supplementation is associated with a higher risk of PCa.
- Aspirin administration for long periods may be associated with a small reduction in PCa risk.
- Dietary folate intake and plasma folate in non-multivitamin users are inversely associated with risk of PCa.
- Folic acid supplementation is associated with increased risk of PCa (age-adjusted hazard ratio = 2.63).
- The role of lycopene and tomato products in preventing PCa is controversial and clinical trial data is needed to better understand this issue.
- Green tea catechins may inhibit progression to PCa in patients with PIN.
Conclusions
Prostate cancer is incredibly complex with respect to its biology, lethal potential, interplay between various risk factors and natural history. It is no surprise that although it seems like an ideal candidate for chemoprevention, clear-cut uncontested level one evidence studies have been difficult to obtain. To some extent, it has also shown the limits of our understanding of the disease biology and its influence by environment or micronutrients, as illustrated by the disappointing failure of some very large trials such as the SELECT trial, although at first sight, the rationale to conduct these trials based on epidemiologic and scientific data was compelling.

Many epidemiologic studies regarding chemoprevention are confounded by variations in geography, accurate reporting of diet, medication use, as well as the inherent difficulties in extrapolating conclusions from small study populations.

A current trend in medicine is to focus on disease prevention but, in PCa, the interplay of complex environmental and genetic factors have made this difficult. Although data linking specific foods and dietary supplements with PCa incidence remain unclear, the impact of diet on PCa development should not be ignored. Similarly, the impact of drugs such as 5αRIs should not be ignored either, as some have been demonstrated as effective chemopreventive agents both in primary and also interestingly, for secondary chemoprevention.

In conclusion, PCa prevention is undoubtedly a complex issue, and no clear strategies apply to all patients. There is plenty of room for additional research in this field and this should be encouraged, despite the occasionally disappointing results that have been reported.

Financial & competing interests disclosure
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