Nutraceuticals and prostate cancer prevention: a current review

Greg Trottier, Peter J. Boström, Nathan Lawrentschuk and Neil E. Fleshner

Abstract | Nutraceuticals are 'natural' substances isolated or purified from food substances and used in a medicinal fashion. Several naturally derived food substances have been studied in prostate cancer in an attempt to identify natural preventative therapies for this disease. Vitamin E, selenium, vitamin D, green tea, soy, and lycopene have all been examined in human studies. Other potential nutraceuticals that lack human data, most notably pomegranate, might also have a preventative role in this disease. Unfortunately, most of the literature involving nutraceuticals in prostate cancer is epidemiological and retrospective. The paucity of randomized control trial evidence for the majority of these substances creates difficulty in making clinical recommendations particularly when most of the compounds have no evidence of toxicity and occur naturally. Despite these shortcomings, this area of prostate cancer prevention is still under intense investigation. We believe many of these 'natural' compounds have therapeutic potential and anticipate future studies will consist of well-designed clinical trials assessing combinations of compounds concurrently.

Trottier, G. *et al. Nat. Rev. Urol.* advance online publication 8 December 2009; doi:10.1038/nrurol.2009.234

Introduction

Prostate cancer is a highly prevalent disease in North America, Western Europe, Eastern Europe and Scandinavia, much more so than in many other regions of the world where diet and lifestyle are markedly different. Indeed, such factors can have a marked effect on the epidemiology of this disease. The classic example is the Japanese man who immigrates to North America, adopts the local diet and lifestyle and gains a higher risk of developing prostate cancer compared to men in his homeland.[1] Such cases illustrate the influence of environment as well as genotype on prostate cancer risk and give credence to efforts to identify and target such factors in prostate cancer prevention. The long time from diagnosis to death from disease, coupled with a high incidence, bring prostate cancer to the fore for primary, secondary and tertiary prevention strategies. As such, successful prevention can manifest as reductions in incidence, recurrence, morbidity or progression of the disease.

Prevention strategies can be directed at almost all aspects of a patient's life. Dietary modification is an obvious target and can include modifications to a patient's normal intake or the addition of natural foods or supplements with anticancer properties. The term 'nutraceutical', coined in 1989, commonly describes natural foods or supplements with therapeutic effects.[2] The Bureau of Nutritional Sciences, of the Food Directorate of Health Canada has defined 'nutraceuticals' and 'functional foods' (Box 1).[3] For the purpose of this Review, we have incorporated functional foods under the umbrella of nutraceuticals.

Competing interests
The authors declare no competing interests.

The study of nutraceuticals in prostate cancer prevention is an important area of study because between 43%[4] and 80%[5] of patients with prostate cancer are on some form of alternative therapy. These individuals include those with a strong family history of prostate cancer, those on active surveillance, and those who have failed active prostate cancer treatments or are on androgen deprivation who seek to delay disease progression by natural means.

This Review focuses on primary, secondary and tertiary prevention studies in prostate cancer using nutraceuticals. Chemoprevention of prostate cancer with 5-α-reductase inhibitors, statins, nonsteroidal anti-inflammatories and other pharmaceuticals will not be addressed and we refer readers to recent reviews for updates on these topics.[6–8] We will emphasize the human studies involving vitamin E, selenium, vitamin D, green tea, soy, and lycopene. We then briefly discuss other promising agents, and the future prospects for clinical trials in this setting.

Vitamin D

Vitamin D is a potent biological agent with several important physiological functions, including mineral metabolism. The active form of vitamin D, 1,25$(OH)_2$-D; calcitriol, is produced by two hydroxylation cycles (liver and kidney) of vitamin D_3 (cholecalciferol), which is synthesized in skin under the action of ultraviolet B radiation.[9] The term 'vitamin' is actually misleading, as cholecalciferol is a pro-hormone to calcitriol, which mediates its physiological actions through the vitamin D_3 receptor (VDR), located in the nuclei of cells.[9] In addition to the classic physiological functions of vitamin D

Division of Urology, Department of Surgical Oncology, University Health Network, University of Toronto, Princess Margaret Hospital, 610 University Avenue 3-130, Toronto, ON M5G 2M9, Canada (**G. Trottier, P. J. Boström, N. Lawrentschuk, N. E. Fleshner**).

Correspondence to: N. Lawrentschuk nathan.lawrentschuk@uhn.on.ca

Key points

- Several naturally derived food substances have been studied in prostate cancer in an attempt to identify natural preventative therapies for this disease
- Vitamins E and D, selenium, green tea, soy, and lycopene remain the most promising nutraceuticals for prostate cancer prevention
- Recent data from large trials have largely been disappointing regarding nutraceuticals and prostate cancer prevention
- We should, however, be careful about ruling out many nutraceuticals, as the evidence against use is not strong and most randomized controlled trials are underpowered to detect positive effects
- Additional, well-designed placebo-controlled trials with adequate power and relevant clinical end points are required and many are being undertaken
- Most trials have taken place in patients with recurrence or castration-resistant disease; more studies are needed in these men, and in those on active surveillance or receiving adjuvant therapy

Box 1 | Nutraceuticals and functional foods

Nutraceutical

"A product isolated or purified from foods that is generally sold in medicinal forms not usually associated with the food. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease."

Functional food

"[A food] consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions."

Definitions from the Bureau of Nutritional Sciences, of the Food Directorate of Health Canada.[3]

(calcium homeostasis and bone metabolism), calcitriol controls cell differentiation and proliferation in a variety of tumor cells.[10] Interestingly, autocrine–paracrine type vitamin D production has been seen in non-kidney tissues, including prostate cells.[9,10] VDR is also present in prostate cells (benign and malignant) and human prostate cancer cell lines respond to vitamin D by growth restriction.[10]

The primary source of vitamin D in western countries is sunlight exposure and only a diminutive quantity is derived from diet.[9] By contrast, diet in other parts of the world can be very rich in vitamin D (in Japan, for example, dietary vitamin D levels are extremely high, most probably owing to high fish consumption).[9] Other factors contribute to lower vitamin D levels in certain populations, such as the elderly (less sun exposure, thinner epidermis), individuals with darker skin (less penetration of ultraviolet B) and physically inactive individuals (less sun exposure, catabolic bone metabolism). The hypothesized link between vitamin D and prostate cancer dates back to 1990, when Shwartz and Hulka[11] suggested that vitamin D is needed to control prostate cell differentiation and that vitamin D deficiency leads to progression of early precancerous lesions to clinical cancers. This hypothesis was supported by the association of several prostate cancer risk factors—advanced age, black race and residence at high latitude—with low serum vitamin D levels. Furthermore, some populations at low risk of prostate cancer (for example, Japanese men) are known to have exceptionally high serum vitamin D levels.[11]

Since this original hypothesis, a great number of epidemiological studies have examined the role of vitamin D in prostate carcinogenesis. Multiple studies have demonstrated that increased geographic ultraviolet radiation is associated with decreased prostate cancer incidence and mortality,[12–18] the effect being strongest in counties above 40°N latitude.[15] By contrast, studies evaluating the association between serum vitamin D levels and subsequent prostate cancer risk have reported variable and conflicting results. A total of 10 such reports are reviewed in Table 1. All these nested case–control studies evaluated the association between vitamin D (measured as 25(OH)-D [calcidiol] levels) and prostate cancer risk. Four of the eight studies conducted in the USA showed no significant association between vitamin D levels and prostate cancer.[19–22] In one report, prostate cancer cases had modestly, but significantly, lower 25(OH)-D levels compared to controls and the effect was greatest in men older than 57 years.[23] Positive results were also found in two Scandinavian studies. Finnish researchers showed that men with 25(OH)-D levels below the median had an odds ratio for prostate cancer of 1.7 (compared to men with levels above the median);[24] the difference in risk was most pronounced in younger patients and for nonlocalized tumors. Another Scandinavian study demonstrated a parabolic risk association: prostate cancer risk was increased at both low and high 25(OH)-D levels.[25]

Two US studies evaluated *VDR* genotype and vitamin D levels in conjunction with prostate cancer risk. Ma *et al.*[26] reported a 57% risk reduction in patients with low 25(OH)-D levels and high-risk *VDR* genotype. In addition to increased prostate cancer risk in men with low 25(OH)-D levels, Li *et al.*[27] demonstrated increased risk of total and more aggressive prostate cancer in patients who had low vitamin D levels and a less-functional *VDR* genotype. Finally, in contrast to most previous studies, Ahn *et al.*[28] showed no significant association between vitamin D levels and overall prostate cancer risk, but higher vitamin D levels were associated with increased risk of aggressive and nonlocalized prostate cancer. Taken together, no clear evidence supports an association between vitamin D levels and prostate cancer risk in populations not deficient in vitamin D. By contrast, in populations from high latitude and among individuals with low vitamin D levels (elderly or inactive individuals), vitamin D supplementation might beneficially affect prostate cancer risk.

Daily ultraviolet B exposure can provide vitamin D_3 levels equivalent up to 10,000 IU.[29] However, sufficient sun exposure is not universal and ultraviolet B potentially causes dermal damage. Although vitamin D doses of 800–4,000 IU per day have shown minimal toxicity,[30] extremely high doses (resulting in serum 25(OH)-D ≥500 nmol/l) may cause life-threatening hypercalcemia.[30] For vitamin D supplementation, vitamin D_3

Table 1 | Case–control studies analyzing the association between vitamin D metabolites and prostate cancer risk

Study	Study population	No. of participants	Disease stage	Outcome variables (mean serum level)	Results
Corder *et al.*[23]	Northern California (USA)	181 cases, 181 controls	65% localized, 12% regional, 16% distant, 7% unknown	25(OH)-D (47–67 nmol/l), $1,25(OH)_2$-D	Lower 1,25(OH)-D associated with PC risk in patients aged >57 years $1,25(OH)_2$-D predicted palpable and anaplastic tumors (not incidental tumors)
Gann *et al.*[20]	Physicians' Health Study (USA)	232 cases, 414 controls	54% localized, 24% regional, 15% distant, 7% unknown	25(OH)-D (60–77 nmol/l), $1,25(OH)_2$-D, vitamin D binding protein	No association between vitamin D metabolites and PC risk
Nomura *et al.*[19]	Hawaii (USA)	136 cases, 136 controls	NA	25(OH)-D, $1,25(OH)_2$-D, calcium phosphorus, parathyroid hormone	Nonsignificant PC risk reduction when highest and lowest 25(OH)-D quartiles were compared (OR 0.8, 95% CI 0.4–1.8)
Ma *et al.*[26]	Physicians' Health Study (USA)	372 cases, 591 controls	NA	25(OH)-D (67–72 nmol/l), $1,25(OH)_2$-D, *VDR* polymorphism (*BSMI* and *TaqI* genotypes)	No association between *VDR* polymorphism and PC risk; men with 25(OH)-D levels below the median had 57% reduction in risk for those with the BB versus the bb genotype (RR 0.43, 95% CI 0.19–0.98)
Ahonen *et al.*[24]	Helsinki Heart Study (Finland)	149 cases, 596 controls	NA	25(OH)-D	Men with 25(OH)-D below the median had OR of 1.7 for PC compared with men above the median; risk was highest in younger men (<52 years) and those with low serum 25(OH)-D (OR 3.1); a higher risk of nonlocalized cancers (OR 6.3) was noted in these men; mean age at diagnosis was 1.8 years higher in patients with high 25(OH)-D concentration compared to those 25(OH)-D below the median
Tuohimaa *et al.*[25]	Scandinavia (Norway, Finland, Sweden)	622 cases, 1,451 controls	65.8% localized, 24.6% nonlocalized, 9.6% not determined	25(OH)-D (Norway 55 nmol/l; Finland 42 nmol/l; Sweden 53 nmol/l)	Both low (≤19 nmol/l) and high (≥80 nmol/l) 25(OH)-D serum concentrations associated with higher PC risk
Jacobs *et al.*[21]	Nutritional Prevention of Cancer trial (USA)	83 cases, 166 controls	NA	25(OH)-D, $1,25(OH)_2$-D	No significant associations; for lowest tertile of plasma 25(OH)-D, adjusted OR for PC was 1.71 (0.68–4.34); for $1,25(OH)_2$-D, OR for PC was 1.44 (0.59–3.52)
Li *et al.*[27]	Physicians' Health Study (USA)	1,066 cases, 1,618 controls	47% aggressive (Gleason ≥7, Whitmore-Jewett stage C or D, metastatic or fatal)	25(OH)-D (79 nmol/l), $1,25(OH)_2$-D, *VDR* polymorphism (*FokI* and *BSMI* genotypes)	Cases with both 25(OH)-D and $1,25(OH)_2$-D below the median had increased risk of aggressive PC (OR 2.1, 95% CI 1.2–3.4); men with low 25(OH)-D levels and the less-functional *FokI* ff genotype had increased risks of total (OR 1.9, 95% CI 1.1–3.3) and aggressive (OR 2.5, 95% CI 1.1–5.8) PC; among men with the *FokI* ff genotype, high plasma 25(OH)-D level was associated with lower risk of total and aggressive PC
Platz *et al.*[22]	Health Professionals Follow-up Study (USA)	460 cases, 460 controls	NA	25(OH)-D (61±19 nmol/l), $1,25(OH)_2$-D	No statistical difference in 25(OH)-D or $1,25(OH)_2$-D levels between cases and controls; OR for PC for top vs bottom quartile of $1,25(OH)_2$-D was 1.25 (95% CI 0.82–1.90; $P_{trend}=0.16$); for 25(OH)-D the OR was 1.19 (95% CI 0.79–1.79; $P_{trend}=0.59$)
Ahn *et al.*[28]	PLCO Cancer Screening Trial (USA)	749 cases, 781 controls	62% Gleason ≥7 or AJCC stage I–II, 26% Gleason ≥8 or AJCC stage III–IV	25(OH)-D (55.9 nmol/l)	In minimally adjusted analysis, significant association between increasing quintile of 25(OH)-D and PC risk ($P=0.04$); nonsignificant trend for increased PC risk in 2 multivariate models ($P=0.10$ and $P=0.20$); no association with nonaggressive disease; significantly increased risk of aggressive disease in 2 multivariate analyses ($P=0.03$ and $P=0.06$)

Abbreviations: $1,25(OH)_2$-D, 1,25-dihydroxycholecalciferol or calcitriol; 25(OH)-D, 25-hydroxycholecalciferol or calcidiol; AJCC, American Joint Committee on Cancer; NA, not available; OR, odds ratio; PC, prostate cancer; PLCO, Prostate, Lung, Colorectal and Ovarian; RR, relative risk; *VDR*, vitamin D receptor.

(cholecalciferol) is recommended (instead of vitamin D_2; ergocalciferol) as it is more effective and more extensively studied.[30] Unfortunately, no long-term prevention trials have evaluated vitamin D supplementation and prostate cancer risk, and most data on vitamin D analogs come from laboratory studies.[31] The only other interventional studies that we are aware of are trials studying the effect of vitamin D in combination with other agents in metastatic castration-resistant prostate cancer, in which results have been variable.[32,33]

Vitamin E

Vitamin E denotes a family of four tocopherols (α-tocopherol is most active in humans) and four tocotrienols with antiproliferative properties. Tocopherols are most abundant in nuts and vegetative oil, whereas tocotrienols are found in palm oil, oat, rye, wheat and rice bran.[34] Classically, the antiproliferative effect of vitamin E is thought to be mediated through antioxidation (neutralization of free radicals). Recent studies have demonstrated additional effects, especially pro-apoptotic activity by maximization of mitochondria-triggered intrinsic apoptosis.[34]

Early studies of a Mediterranean diet rich in vitamin E suggested a possible chemopreventive role in colon carcinogenesis.[35] Further evidence from Switzerland demonstrated that low serum vitamin E levels were associated with increased mortality from prostate

cancer.[36] Observational results from the US Health Professionals cohort suggested that among smokers, vitamin E supplementation resulted in a reduced risk of advanced and fatal prostate cancer (based on questionnaire evaluation of dietary and supplemental vitamin E intake).[37] Similarly, evaluation of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial cohort demonstrated reduced risk of advanced prostate cancer with vitamin E supplementation in smokers.[38] By contrast, the Cancer Prevention Study II Nutrition Cohort did not demonstrate any significant association between vitamin E supplementation and risk of prostate cancer.[39] Lastly, in the NIH–AARP Diet and Health Study, dietary γ-tocopherol, but not vitamin E supplementation, resulted in reduced prostate cancer risk.[40]

Interest in a possible chemopreventive effect of vitamin E on prostate cancer risk was sparked by the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, originally published in 1994, which was designed to study the effect of supplementary vitamin E and β-carotene on lung cancer risk in smokers.[41] Although they found negative results regarding lung cancer prevention, the investigators noted a reduced risk of prostate cancer in the group of patients who received vitamin E. Further analysis of this study cohort after additional follow-up revealed a 32% decrease in prostate cancer incidence.[42] The decrease was noted in clinical but not latent prostate cancer. Most importantly, mortality was 41% lower in the vitamin E study arm.[42] However, prostate cancer was not the primary end point of the study design, and this is a possible source of misleading results.

In January 2009 two important papers were simultaneously published in *The Journal of the American Medical Association* with disappointing results regarding prostate cancer prevention with vitamin E supplementation. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) accrued 35,000 men and randomized them into four groups (selenium, vitamin E, selenium plus vitamin E, and placebo).[43] Among the inclusion criteria were PSA level ≤4 ng/ml and negative digital rectal examination. After a follow-up period of 5.5 years, a total of 1,758 men were diagnosed with prostate cancer, with no significant differences between groups. By contrast, an insignificant trend towards increased risk of prostate cancer was seen in the vitamin E group ($P = 0.06$).[43]

The Physicians' Health Study II randomized 14,641 male physicians in the USA to receive either vitamin E plus vitamin C, vitamin E (plus placebo), vitamin C (plus placebo) or placebo only. In contrast to SELECT, patients were not screened for prostate cancer before enrollment and 1,307 men with a history of cancer were included.[44] After a mean follow-up of 8.0 years, 1,008 new prostate cancers were diagnosed and no significant differences in incidence of prostate cancer (or other cancers) were noted between groups. Explanations for the negative results in these two trials include that a chemopreventive effect of vitamin E is limited only to smokers (only smokers were included in the ATBC study, compared with 3.9% current smokers in Physicians' Health Study II, and 8% in SELECT), and that widespread PSA screening results in high discovery of latent prostate cancers, which dilutes the possible preventive effect of supplementation on clinically significant cancers. In fact, in SELECT approximately 85% of men underwent annual PSA testing and only 7 of 1,758 prostate cancers were metastatic, with a single prostate cancer death.[43]

Lycopene

Lycopene is a carotenoid antioxidant mainly found in tomatoes and is thought to protect against free radicals that can damage DNA and lead to neoplasms. Of all carotenoids, lycopene is the most efficient scavenger of oxygen radicals.[45] In addition to its antioxidant characteristics, lycopene also possesses other mechanisms that interfere with cancer cell signaling.[46]

In 1989 a large cohort study of 14,000 Seventh-day Adventist men who eat a vegetarian diet found that high consumption of tomato products in addition to other foods (beans, lentils, peas, raisins, dates and dried fruit) was independently associated with a reduced prostate cancer risk.[47] This led to several case–control and cohort studies examining the effect of lycopene and tomatoes on prostate cancer risk. Most studies show a reduced risk or a trend towards reduction of prostate cancer risk, particularly with cooked tomatoes, as confirmed in a meta-analysis.[48] Giovannucci's group, using the Health Professionals Follow-up Study, supplied the largest cohort in the meta-analysis, identifying that tomatoes cooked in sauces and associated with fatty foods such as pizza conferred a reduced risk of prostate cancer, whereas unprocessed tomato juice did not.[49,50] Studies on the bioavailability of lycopene have shown that processing tomatoes by heating in oil, as in the production of tomato sauce, results in increased serum levels of lycopene after ingestion.[51,52]

A case–control study assessing serum levels of lycopene and several other carotenoids found that lycopene was the only carotenoid for which serum levels were lower in cases of prostate cancer.[53] This study, along with the cohort study by Giovannucci *et al.*,[49] found that low lycopene serum levels and intake were more strongly associated with aggressive prostate cancer than with less-aggressive prostate cancer. More recent reports from the PLCO screening trial do not support the association between lycopene or tomato intake and prostate cancer.[54,55] This cohort was large (1,338 prostate cancer cases out of 29,361 men screened), and as a result has called into question the association between lycopene and prostate cancer risk. However, a nonsignificant trend for cooked tomato substance intake to reduce prostate cancer risk was noted.

The PLCO investigators[55] and the European Prospective Investigation into Cancer and Nutrition study[56] also measured lycopene in serum samples in a nested case–control fashion and found no association between lycopene levels and prostate cancer risk. The European study did find an association between low lycopene levels and advanced prostate cancer, which was not seen in the PLCO study. No prospective

randomized controlled trials have examined the effect of lycopene on prostate cancer risk, and until such evidence is available, the inconsistencies among the above epidemiologic studies do not support lycopene supplementation. An FDA literature review,[57] even without including the negative PLCO study,[55] concluded that "there was limited credible evidence for a qualified health claim about tomato consumption and a reduced risk of prostate cancer."

Lycopene has also been studied in men with known prostate cancer. Chen *et al.*[58] gave patients with a biopsy diagnosis of prostate cancer a high lycopene diet for 3 weeks before radical prostatectomy and found higher lycopene levels in prostate tissues and serum compared to baseline. On comparison of final pathologic specimens with those from similar patients who did not consume a high tomato diet, they found decreased oxidative damage to the DNA[58] and an increased apoptotic index.[59] In a similar, small, phase II randomized controlled trial, 26 men with newly diagnosed localized prostate cancer were assigned to receive 15 mg of lycopene twice daily for 3 weeks or no supplement before radical prostatectomy.[60] Although this was a very small study with a short treatment period, 11 men (73%) in the intervention group had no involvement of the surgical margins or extraprostatic extension compared with 2 men (18%) in the control group. Likewise, tumors tended to be smaller in the lycopene intervention group. Levels of tissue biomarkers of malignancy did not change with lycopene treatment, but PSA levels decreased in the lycopene-treated group and increased in the control group.[60] Collectively, these studies suggest that lycopene accumulates in the prostate, where it has biochemical activity. However, it is difficult to comment on whether adjuvant lycopene treatment truly affects clinically relevant end points, as the studies in this field are small and biochemical changes do not necessarily translate into clinical outcomes.

Lycopene has also been studied in advanced and metastatic prostate cancer. A randomized trial from India assessed 54 patients with metastatic prostate cancer treated with orchiectomy alone or orchiectomy plus 2 mg of lycopene daily.[61] The lycopene-treated group had more marked reductions in PSA levels at 2 years and better responses on bone scan compared to the control group. By contrast, in an American study in which patients had biochemical failure of prostate cancer after definitive therapy, escalating doses of lycopene from 15 mg to 120 mg daily over 1 year had no effect on PSA doubling time compared with baseline.[62] No effect was found on PSA levels at 1 year in the Indian trial either, suggesting that such an effect might require at least 2 years of treatment with lycopene. Three studies have reported the effects of lycopene in castration-resistant prostate cancer,[63–65] and with the exception of a few cases in each study as well as one case report,[66] the overall results are not promising.

Thus, in summary, no strong evidence recommends lycopene in patients who already have prostate cancer, as randomized placebo-control trials are lacking. Nonetheless, the minimal adverse effects combined with the handful of cases reporting extreme PSA and subjective improvements argue that lycopene should not be totally neglected in the palliative setting. Several combination studies of lycopene and other nutraceutical compounds have also been undertaken and are discussed below.

Soy and isoflavones

Soybeans are a species of legume and a source of phytochemicals that are nutraceuticals.[67] Tofu is derived from soybeans and is common in the Chinese diet. Soy products contain isoflavones, which have structural similarity to estrogen and are thus referred to as phytoestrogens. Like all other nutraceuticals, components of soybeans such as genistein, a tyrosine kinase inhibitor, produce anticancer effects including apoptosis and inhibition of cell growth in prostate cancer cell lines and animal studies.[67] Human studies have also shown an increase in urine excretion of estrogen[68] and reduced postprostatectomy COX-2 expression,[69] suggesting inflammatory and steroid pathway modulation in soy-supplemented patients.

As a result of the low risk of prostate cancer in Asian men and the high consumption of soy products in these cultures, many studies, including an exhaustive list of case–control and cohort studies, have investigated the association between soy and prostate cancer. Yan and Spitznagel[70] summarize and critically review this evidence in an up-to-date meta-analysis, which includes nine case–control studies and five cohort studies. Collectively, the results show a relative risk/odds ratio for prostate cancer of 0.74 (95% CI 0.63–0.89; $P = 0.01$) with consumption of all types of soy products. Specifically, studies using nonfermented soy revealed a significant reduction in prostate cancer risk, whereas studies using fermented soy (miso soup or nattō) or isoflavone supplementation did not find significant results. In fact, the combined relative risk/odds ratio of fermented soy studies was 1.10 (95% CI 0.76–1.57). On further analysis of the isoflavone supplementation studies, significant risk reductions were found in Asian men, while studies in Western populations yielded no effect on prostate cancer risk. In summary, this meta-analysis suggests that nonfermented soy has chemopreventative properties while fermented soy does not, and that isoflavones have a differential effect in Asian men compared to Western men. No laboratory studies have established a mechanism for these differing outcomes.

In healthy men, soy does not seem to have an effect on PSA levels.[71,72] PSA responses in patients with prostate cancer treated with a variety of soy products in randomized controlled trials are mostly positive, with three studies showing a reduction in PSA[73–75] and one showing an improvement in the free:total ratio of PSA.[73] Hussain *et al.* showed a prolongation of PSA doubling time (PSADT) in patients treated with soy products while they were on active surveillance or with prostate cancer recurrence.[76] One study suggested no clinical effect of soy supplementation as no patient had a more

than 50% reduction in PSA level.[77] However, PSADT was not assessed in this study and could be relevant as Hussain and colleagues[76] also failed to see a greater than 50% decrease in PSA levels, yet did find an improvement in PSADT in soy-treated patients. Interestingly, one randomized controlled trial assessing prostate biopsy specimens from 58 patients on active surveillance or at high risk of prostate cancer found that treatment with soy protein or alcohol-washed soy protein reduced the detection of prostate cancer at 6 months, compared with milk-protein-treated patients.[78] Alcohol-washed soy protein also affected levels of prostate cancer markers, whereas nonwashed soy did not. This example illustrates the effects of soy on both primary and tertiary prevention of prostate cancer, and a larger confirmatory study could have important implications for patients on active surveillance.

Overall, the evidence for soy alone in prostate cancer prevention is moderate in strength. Soy has shown benefit for primary prevention of prostate cancer in uncontrolled studies, as well as in randomized controlled trials in patients on active surveillance or with recurrence of prostate cancer. Unfortunately, most trials in this setting have relied on PSA level as a surrogate for disease activity.

Green tea

Green tea is a commonly consumed beverage in Asia that is derived from the plant *Camellia sinensis*. The medicinal components of green tea are polyphenol antioxidants termed catechins, comprising four principle compounds: epicatechin, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate (EGCG).[79] *In vitro* and animal studies with EGCG, the major catechin in green tea, have implicated this compound in many anticancer signaling processes including inhibition of 5-α-reductase.[80] Unfortunately, in epidemiological studies green tea has been less consistent as an anticancer therapy.

Four cohort studies,[81–84] two case–control studies[85,86] and one randomized controlled trial have evaluated the association between green tea and prostate cancer risk.[87,88] A Chinese case–control study demonstrated a dose-dependent reduction in prostate cancer risk starting at 1–3 cups per day of green tea.[85] Another case–control study from Japan revealed only a trend towards reduced risk of prostate cancer, with an odds ratio of 0.67 and a very wide confidence interval, when more than 10 cups of tea per day were consumed.[86] By contrast, two cohort studies clearly show no association between green tea consumption and prostate cancer risk.[81,82] Patients in these studies were not stratified by disease stage, which might be an important factor.

A more recent cohort study by Kurahashi *et al.*[83] has established a reduction in the incidence of more advanced prostate cancer, with no effect on low-stage prostate cancer, with consumption of 5 or more cups of green tea per day. As these authors note, the inconsistencies in the literature might be amplified by a lack of disease-stage stratification. In the aforementioned positive Chinese case–control study,[85] over 70% of patients presented with advanced disease, which could explain why they had more favorable results than individuals in the Japanese case–control study,[86] in which prostate cancer screening and lower-stage disease at presentation were more common. Finally, a double-blind, placebo-controlled trial examined the effect of purified green tea catechins (600 mg/day) on prostate cancer incidence in patients with high-grade prostatic intraepithelial neoplasia.[87,88] The number of patients was small ($n = 60$) and the follow-up was short (1 year for the initial report, and approximately 2 years for a follow-up report). One of 30 men in the green tea group developed prostate cancer at 1 year, whereas 9 of 30 men in the placebo group developed prostate cancer at 1 year. Although this trial is small and could suffer from an alpha error (false-positive results), the authors plan to undertake a larger randomized controlled trial. Importantly, the above studies indicate that there seems to be no harm in using green tea at normal daily intake levels.

Two clinical trials have also evaluated green tea in the treatment of castration-resistant prostate cancer[89,90] with neither study showing clinically relevant outcomes. Choan and colleagues[90] noted that the concentration of EGCG that shows anticancer properties in laboratory studies is an order of magnitude greater than that achieved by the highest tolerable oral dose of 6 g used in the phase II study by Jatoi *et al.*[89] The higher oral doses of EGCG used in this study produced nausea, emesis, insomnia, fatigue, diarrhea, abdominal pain and confusion in 69% of patients, with some grade 3 and 4 events. The doses used in the study by Jatoi *et al.*[89] are substantially higher than the usual daily intake of green tea and than the doses used in the prevention studies described above, in which no adverse effects were described.

In summary, green tea might have some benefit in the prevention of prostate cancer at normal daily doses (5–10 cups per day), and purified EGCG can be used as an alternative to brewed tea. However, a large randomized placebo-controlled trial is certainly needed before any clear recommendations can be made. With respect to treatment of prostate cancer, we do not know the effect of these agents on individuals with hormone-sensitive prostate cancer (such as patients on active surveillance) or the effect on recurrence after primary treatment. Reasonable evidence suggests that green tea and its derivatives have little role in the treatment of castration-resistant prostate cancer.

Combination studies

Combining the above nutraceuticals in a preventative cocktail is a strategy that would intuitively provide an additive or synergistic effect. Of studies examining combinations of the various nutraceuticals mentioned above, we have summarized the results of six controlled trials in Table 2. The results from all studies are positive in one form or another except for the combination arm of SELECT[44] and the combined vitamin E, selenium and soy arm from the Canadian trial.[91] Surprisingly, outcomes are not clearly better than those seen in studies of the individual compounds suggesting no additive benefit of

Table 2 | Trials examining combinations of nutraceutical agents

Study	Agents used	Study population	Design	Primary end points	Clinical outcomes
Gazioano *et al.*[44] (SELECT trial)	Vitamin E, selenium	8,863 men without PC	RCT with 4 arms: vitamin E or selenium or combination vs placebo for 3 years	PC	No support for the hypothesis that combination therapy with vitamin E and selenium prevents PC
Fleshner *et al.*[91]	Vitamin E, selenium, soy	303 men with high-grade PIN in each study arm	RCT with 2 arms: combination vs placebo for 3 years	Biopsy-proven PC	No support for the hypothesis that combination therapy with vitamin E, selenium, and soy prevents progression from high-grade PIN to PC
Ornish *et al.*[97]	Vegan diet plus tofu/ fortified soy, fish oil, vitamin E, selenium, vitamin C (also exercise and stress management)	93 men with localized PC, Gleason <6, not wanting local treatment	RCT with 2 arms: lifestyle intervention vs standard care for 12 months	Absolute PSA	Significant PSA changes at 12 months: 4% decrease from baseline in the treatment group and 6% increase in the control group
Vaishampayan *et al.*[98]	Soy isoflavones, lycopene	71 men with biochemical recurrence after local therapy, with or without hormone therapy	Phase II trial with 2 arms: lycopene alone or lycopene plus isoflavones for up to 6 months	Toxicity, partial or complete PSA response	No objective or complete responses (PSA reduction >50%); PSA stabilization in 95% of patients in the lycopene arm and only 67% in the combined arm; rate of PSA rise significantly decreased in both arms compared to baseline
Kranse *et al.*[99]	Dietary supplement known as 'Verum' (contains vitamin E, selenium, green tea, isoflavones, carotinoids)	37 men with biochemical recurrence after local therapy	RCT with 2 arms and crossover: supplement vs placebo for 6 weeks	Total and free PSA, PSADT, testosterone and DHT levels	Overall no PSADT increase, but free PSADT did increase; testosterone and DHT levels decreased in the treatment group
Schöder *et al.*[100]	Soy, isoflavones, lycopene, silymarin, many antioxidants	49 men with biochemical recurrence after local therapy	RCT with 2 arms and crossover: supplement vs placebo for 10 weeks	PSADT, PSA slope	PSADT was 1,150 days in the treatment group and 44 days in the placebo group; PSA slope was significantly steeper in the treatment group only when intention to treat analysis was not used

Abbreviations: DHT, dihydrotestosterone; PC, prostate cancer; PIN, prostatic intraepithelial neoplasia; PSADT, PSA doubling time; RCT, randomized controlled trial.

combining different agents. Four of the six studies take place in patients who had already been diagnosed with prostate cancer and are limited by the use of PSA as a surrogate for disease progression.

Other potential nutraceuticals

Several nutraceuticals have only been studied in prostate cancer cell lines and animal experiments. For full details, we refer readers to an excellent review by Syed *et al.*[80] By way of example, delphinidin from delphinium flowers, lupeol from several fruits and vegetables, and fisetin also from many fruits and vegetables have all been shown to have anticancer activity in laboratory studies. Properties of these compounds vary from antioxidant scavenging, to anti-inflammatory, antiangiogenic and apoptotic functions. We suspect that human clinical studies with these compounds will shortly be underway, although none are currently registered.

Several other nutraceuticals (garlic, citrus pectin, shitake mushroom, silibinin) with positive effects against prostate cancer in laboratory experiments have been tested in humans.[92] Most studies produced negative results using nonrandomized, uncontrolled designs, and for this reason most of these agents have not been pursued further (reviewed by Van Patten *et al.*[92]).

Pomegranate (*Punica granatum*) is a fruit rich in polyphenolic compounds, which have the highest antioxidant activity of the compounds discussed thus far, and has recently gained interest in the field of prostate cancer (reviewed by Lansky and Newman[93]). With respect to active ingredients, the seed, juice, fruit, peel, roots, bark, leaves, and flowers may all contribute. Many known anticancer compounds have been purified from the pomegranate plant, such as γ-tocopherol, catechins, anthocyanidins, flavols and flavones to name a few.[93] Pomegranate fruit extracts have also shown anticancer activity in prostate cancer cell lines.[80] A recent phase II, Simon two-stage clinical trial investigated the effect of pomegranate juice (237 ml [8 oz] per day) on 46 men with biochemical recurrence after definitive therapy for prostate cancer.[94] PSADT, the main clinical end point, was compared before pomegranate treatment and at several time points after daily pomegranate intake. At 24 months, 7 patients had a decline in PSA and were not eligible for calculation of PSADT; the PSADT of the remaining patients had increased to 37.0 ± 53 months from a baseline of 15.0 ± 11.1 months (P <0.0001). While the results of this study are encouraging, a large double-blind, placebo-controlled trial is underway with two doses of pomegranate to hopefully strengthen the evidence for pomegranate juice in the treatment of prostate cancer recurrence. Unlike lycopene and other nutraceuticals, the role of pomegranate is being investigated with more poise in the form of a subsequent well-designed, placebo-controlled trial rather than a plethora of epidemiologic studies.

Future prospects

The current status of nutraceuticals for the prevention of prostate cancer is in flux. As recently outlined by Gann,[95] epidemiology teaches that every statistical association has only three possible explanations: bias, chance, and cause. Regarding nutraceuticals and prostate cancer prevention, first-generation phase III trials were too reliant on biased interpretation of prior research, and second-generation trials might have been too reliant on chance; yet, we have every reason to believe that the next generation will have a firmer basis for causal hypotheses. The issue of contamination of placebo arms in randomized controlled trials is also yet to be resolved. Gann[95] recommends that until additional positive data are available, physicians should not recommend selenium or vitamin E—or any other antioxidant supplement—to their patients for the prevention of prostate cancer.

Interestingly, Lawlor and colleagues[96] also recognized the disparity between observational studies and randomized trial evidence regarding the health effects of antioxidant vitamins. They concluded that this disparity is probably explained by a failure to appreciate the complex and important differences between adults with high vitamin concentrations and those with lower concentrations. High intake of antioxidant vitamins might not be causally related to diseases such as prostate cancer, but rather serves as a proxy indicator of a host of factors that protect against these diseases.

We also agree with all the conclusions of Lawlor and colleagues,[96] who state that, when feasible, randomized controlled trials provide the most robust estimate of a causal effect. Such studies, however, are not always feasible. Randomized controlled trials are expensive and raise ethical concerns; observational studies are, therefore, used to direct investigators to the interventions that would be most appropriate for assessment in trials. Thus, widespread abandonment of observational studies for randomized controlled trials is not necessarily the solution. Careful design and analysis of observational epidemiological studies can ensure that they remain a useful method for generating and testing hypotheses that ultimately might improve public health.

Conclusions

We conclude from our review that physicians should be careful about ruling out many nutraceuticals as the evidence against use is not strong and most randomized controlled trials are underpowered to detect positive associations. Unfortunately, many early studies on nutraceuticals were poorly designed, and provided inconsistent results. This fact has led to sweeping claims being made, which have either ruled in or out particular nutraceuticals on the basis of low-quality evidence. For example, when inconsistencies between case–control studies exist, with the majority showing no significant effect of a dietary substance on prostate cancer risk, one can hardly make any reasonable conclusions as to the effectiveness of the substance. The only way to settle such debates is through a well-designed, placebo-controlled trial with adequate power and relevant clinical end points. Clearly, in the field of prostate cancer, more studies are needed in men on active surveillance or receiving adjuvant therapy, and in individuals with biochemical recurrence or castration-resistant disease. Encouragingly, at least 40 ongoing randomized controlled trials are registered on clinicaltrials.gov, investigating various nutraceuticals in prostate cancer, including studies on vitamin E, selenium, vitamin D, green tea, soy and lycopene among others. These trials will hopefully provide high-quality evidence to enable better recommendations to be made.

Review criteria

A literature search was performed using the MEDLINE and EMBASE databases. Search terms included "nutraceuticals", "dietary supplement", "soy", "isoflavone", "lycopene", "green tea", "vitamin D", "vitamin E", "selenium", "pomegranate", "diet", "diet therapy", "diet supplements", "vitamins", "herbal", "antioxidant", "chemoprevention" and "prostate cancer". The literature we chose focused on human studies and when necessary laboratory studies. We restricted our search to studies in the English language and did not set any date limits. We also used recent reviews and discussions from original papers to retrieve articles.

1. Shimizu, H. *et al.* Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br. J. Cancer* **63**, 963–966 (1991).
2. Kalra, E. K. Nutraceutical–definition and introduction. *AAPS PharmSci.* **5**, E25 (2003).
3. Health Canada. http://www.hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/nutra-funct_foods-nutra-fonct_aliment-eng.php, accessed August 26th 2009 (Ottawa, 1998).
4. Lippert, M. C., McClain, R., Boyd, J. C. & Theodorescu, D. Alternative medicine use in patients with localized prostate carcinoma treated with curative intent. *Cancer* **86**, 2642–2648 (1999).
5. Nam, R. K. *et al.* Prevalence and patterns of the use of complementary therapies among prostate cancer patients: an epidemiological analysis. *J. Urol.* **161**, 1521–1524 (1999).
6. Hamilton, R. J. & Freedland, S. J. Rationale for statins in the chemoprevention of prostate cancer. *Curr. Urol. Rep.* **9**, 189–196 (2008).
7. Rittmaster, R. S., Fleshner, N. E. & Thompson, I. M. Pharmacological approaches to reducing the risk of prostate cancer. *Eur. Urol.* **55**, 1064–1073 (2009).
8. Colli, J. L. & Amling, C. L. Chemoprevention of prostate cancer: what can be recommended to patients? *Curr. Urol. Rep.* **10**, 165–171 (2009).
9. Schwartz, G. G. Vitamin D and the epidemiology of prostate cancer. *Semin. Dial.* **18**, 276–289 (2005).
10. Krishnan, A., Peehl, D. & Feldman, D. Inhibition of prostate cancer growth by vitamin D: regulation of target gene expression. *J. Cell Biochem.* **88**, 363–371 (2003).
11. Schwartz, G. & Hulka, B. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). *Anticancer Res.* **10**, 1307–1311 (1990).
12. Hanchette, C. & Schwartz, G. Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer* **70**, 2861–2869 (1992).
13. Kafadar, K. Geographic trends in prostate cancer mortality: an application of spatial smoothers and the need for adjustment. *Ann. Epidemiol.* **7**, 35–45 (1997).
14. Grant, W. An estimate of premature cancer mortality in the U. S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* **94**, 1867–1875 (2002).
15. Schwartz, G. & Hanchette, C. UV, latitude, and spatial trends in prostate cancer mortality: all sunlight is not the same (United States). *Cancer Causes Control* **17**, 1091–1101 (2006).
16. Di Silverio, F., La Pera, G. & Tenaglia, R. Age-adjusted mortality rate and regional distribution for prostatic carcinoma in Italy between 1969 and 1978. *Prostate* **3**, 631–636 (1982).
17. John, E., Dreon, D., Koo, J. & Schwartz, G. Residential sunlight exposure is associated with

a decreased risk of prostate cancer. *J. Steroid Biochem. Mol. Biol.* **89–90**, 549–552 (2004).
18. John, E., Schwartz, G., Koo, J., Van Den Berg, D. & Ingles, S. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Res.* **65**, 5470–5479 (2005).
19. Nomura, A. *et al.* Serum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States). *Cancer Causes Control* **9**, 425–432 (1998).
20. Gann, P. *et al.* Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. *Cancer Epidemiol. Biomarkers Prev.* **5**, 121–126 (1996).
21. Jacobs, E. *et al.* Plasma levels of 25-hydroxyvitamin D, 1, 25-dihydroxyvitamin D and the risk of prostate cancer. *J. Steroid Biochem. Mol. Biol.* **89–90**, 533–537 (2004).
22. Platz, E., Leitzmann, M., Hollis, B., Willett, W. & Giovannucci, E. Plasma 1, 25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. *Cancer Causes Control* **15**, 255–265 (2004).
23. Corder, E. *et al.* Vitamin D and prostate cancer: a prediagnostic study with stored sera. *Cancer Epidemiol. Biomarkers Prev.* **2**, 467–472 (1993).
24. Ahonen, M., Tenkanen, L., Teppo, L., Hakama, M. & Tuohimaa, P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* **11**, 847–852 (2000).
25. Tuohimaa, P. *et al.* Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int. J. Cancer* **108**, 104–108 (2004).
26. Ma, J. *et al.* Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. *Cancer Epidemiol. Biomarkers Prev.* **7**, 385–390 (1998).
27. Li, H. *et al.* A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. *PLoS Med.* **4**, e103 (2007).
28. Ahn, J. *et al.* Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J. Natl Cancer Inst.* **100**, 796–804 (2008).
29. Vieth, R. Vitamin D and cancer mini-symposium: the risk of additional vitamin D. *Ann. Epidemiol.* **19**, 441–445 (2009).
30. Garland, C., Gorham, E., Mohr, S. & Garland, F. Vitamin D for cancer prevention: global perspective. *Ann. Epidemiol.* **19**, 468–483 (2009).
31. Chen, T. C., Holick, M. F., Lokeshwar, B. L., Burnstein, K. L. & Schwartz, G. G. Evaluation of vitamin D analogs as therapeutic agents for prostate cancer. *Recent Results Cancer Res.* **164**, 273–288 (2003).
32. Newsom-Davis, T., Kenny, L., Ngan, S., King, J. & Waxman, J. The promiscuous receptor. *BJU Int.* **104**, 1204–1207 (2009).
33. Beer, T. *et al.* Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. *J. Clin. Oncol.* **25**, 669–674 (2007).
34. Constantinou, C., Papas, A. & Constantinou, A. Vitamin E and cancer: an insight into the anticancer activities of vitamin E isomers and analogs. *Int. J. Cancer* **123**, 739–752 (2008).
35. Berrino, F. & Muti, P. Mediterranean diet and cancer. *Eur. J. Clin. Nutr.* **43** (Suppl. 2), 49–55 (1989).
36. Eichholzer, M., Stähelin, H., Gey, K., Lüdin, E. & Bernasconi, F. Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. *Int. J. Cancer* **66**, 145–150 (1996).
37. Chan, J. *et al.* Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. *Cancer Epidemiol. Biomarkers Prev.* **8**, 893–899 (1999).
38. Kirsh, V. *et al.* Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J. Natl Cancer Inst.* **98**, 245–254 (2006).
39. Rodriguez, C. *et al.* Vitamin E supplements and risk of prostate cancer in U. S. men. *Cancer Epidemiol. Biomarkers Prev.* **13**, 378–382 (2004).
40. Wright, M. *et al.* Supplemental and dietary vitamin E intakes and risk of prostate cancer in a large prospective study. *Cancer Epidemiol. Biomarkers Prev.* **16**, 1128–1135 (2007).
41. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N. Engl. J. Med.* **330**, 1029–1035 (1994).
42. Heinonen, O. *et al.* Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J. Natl Cancer Inst.* **90**, 440–446 (1998).
43. Lippman, S. *et al.* Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* **301**, 39–51 (2009).
44. Gaziano, J. *et al.* Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA* **301**, 52–62 (2009).
45. Di Mascio, P., Kaiser, S. & Sies, H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch. Biochem. Biophys.* **274**, 532–538 (1989).
46. Wertz, K., Siler, U. & Goralczyk, R. Lycopene: modes of action to promote prostate health. *Arch. Biochem. Biophys.* **430**, 127–134 (2004).
47. Mills, P. K., Beeson, W. L., Phillips, R. L. & Fraser, G. E. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer* **64**, 598–604 (1989).
48. Etminan, M., Takkouche, B. & Caamano-Isorna, F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. *Cancer Epidemiol. Biomarkers Prev.* **13**, 340–345 (2004).
49. Giovannucci, E. *et al.* Intake of carotenoids and retinol in relation to risk of prostate cancer. *J. Natl Cancer Inst.* **87**, 1767–1776 (1995).
50. Giovannucci, E., Rimm, E. B., Liu, Y., Stampfer, M. J. & Willett, W. C. A prospective study of tomato products, lycopene, and prostate cancer risk. *J. Natl Cancer Inst.* **94**, 391–398 (2002).
51. Gartner, C., Stahl, W. & Sies, H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *Am. J. Clin. Nutr.* **66**, 116–122 (1997).
52. Stahl, W. & Sies, H. Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. *J. Nutr.* **122**, 2161–2166 (1992).
53. Gann, P. H. *et al.* Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res.* **59**, 1225–1230 (1999).
54. Kirsh, V. A. *et al.* A prospective study of lycopene and tomato product intake and risk of prostate cancer. *Cancer Epidemiol. Biomarkers Prev.* **15**, 92–98 (2006).
55. Peters, U. *et al.* Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol. Biomarkers Prev.* **16**, 962–968 (2007).
56. Key, T. J. *et al.* Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. *Am. J. Clin. Nutr.* **86**, 672–681 (2007).
57. Kavanaugh, C. J., Trumbo, P. R. & Ellwood, K. C. The U. S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. *J. Natl Cancer Inst.* **99**, 1074–1085 (2007).
58. Chen, L. *et al.* Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *J. Natl Cancer Inst.* **93**, 1872–1879 (2001).
59. Kim, H. S. *et al.* Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. *Nutr. Cancer* **47**, 40–47 (2003).
60. Kucuk, O. *et al.* Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol. Biomarkers Prev.* **10**, 861–868 (2001).
61. Ansari, M. S. & Gupta, N. P. A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer. *BJU Int.* **92**, 375–378 (2003).
62. Clark, P. E. *et al.* Phase I–II prospective dose-escalating trial of lycopene in patients with biochemical relapse of prostate cancer after definitive local therapy. *Urology* **67**, 1257–1261 (2006).
63. Ansari, M. S. & Gupta, N. P. Lycopene: a novel drug therapy in hormone refractory metastatic prostate cancer. *Urol. Oncol.* **22**, 415–420 (2004).
64. Jatoi, A. *et al.* A tomato-based, lycopene-containing intervention for androgen-independent prostate cancer: results of a Phase II study from the North Central Cancer Treatment Group. *Urology* **69**, 289–294 (2007).
65. Schwenke, C., Ubrig, B., Thurmann, P., Eggersmann, C. & Roth, S. Lycopene for advanced hormone refractory prostate cancer: a prospective, open phase II pilot study. *J. Urol.* **181**, 1098–1103 (2009).
66. Matlaga, B. R., Hall, M. C., Stindt, D. & Torti, F. M. Response of hormone refractory prostate cancer to lycopene. *J. Urol.* **166**, 613 (2001).
67. Jian, L. Soy, isoflavones, and prostate cancer. *Mol. Nutr. Food Res.* **53**, 217–226 (2009).
68. Hamilton-Reeves, J. M., Rebello, S. A., Thomas, W., Slaton, J. W. & Kurzer, M. S. Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer. *J. Nutr.* **137**, 2258–2263 (2007).
69. Swami, S. *et al.* Inhibition of prostaglandin synthesis and actions by genistein in human prostate cancer cells and by soy isoflavones in prostate cancer patients. *Int. J. Cancer* **124**, 2050–2059 (2009).
70. Yan, L. & Spitznagel, E. L. Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis. *Am. J. Clin. Nutr.* **89**, 1155–1163 (2009).

71. Urban, D. *et al.* The effect of isolated soy protein on plasma biomarkers in elderly men with elevated serum prostate specific antigen. *J. Urol.* **165**, 294–300 (2001).
72. Adams, K. F., Chen, C., Newton, K. M., Potter, J. D. & Lampe, J. W. Soy isoflavones do not modulate prostate-specific antigen concentrations in older men in a randomized controlled trial. *Cancer Epidemiol. Biomarkers Prev.* **13**, 644–648 (2004).
73. Dalais, F. S. *et al.* Effects of a diet rich in phytestrogens on prostate-specific antigen and sex hormones in men diagnosed with prostate cancer. *Urology* **64**, 510–515 (2004).
74. Spentzos, D. *et al.* Minimal effect of a low-fat/high soy diet for asymptomatic, hormonally naive prostate cancer patients. *Clin. Cancer Res.* **9**, 3282–3287 (2003).
75. Kumar, N. B. *et al.* The specific role of isoflavones in reducing prostate cancer risk. *Prostate* **59**, 141–147 (2004).
76. Hussain, M. *et al.* Soy isoflavones in the treatment of prostate cancer. *Nutr. Cancer* **47**, 111–117 (2003).
77. deVere White, R. W. *et al.* Effects of a genistein-rich extract on PSA levels in men with a history of prostate cancer. *Urology* **63**, 259–263 (2004).
78. Hamilton-Reeves, J. M., Rebello, S. A., Thomas, W., Kurzer, M. S. & Slaton, J. W. Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer. *Nutr. Cancer* **60**, 7–13 (2008).
79. Adhami, V. M. & Mukhtar, H. Anti-oxidants from green tea and pomegranate for chemoprevention of prostate cancer. *Mol. Biotechnol.* **37**, 52–57 (2007).
80. Syed, D. N., Suh, Y., Afaq, F. & Mukhtar, H. Dietary agents for chemoprevention of prostate cancer. *Cancer Lett.* **265**, 167–176 (2008).
81. Severson, R. K., Nomura, A. M., Grove, J. S. & Stemmermann, G. N. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res.* **49**, 1857–1860 (1989).
82. Kikuchi, N. *et al.* No association between green tea and prostate cancer risk in Japanese men: the Ohsaki Cohort Study. *Br. J. Cancer* **95**, 371–373 (2006).
83. Kurahashi, N., Sasazuki, S., Iwasaki, M., Inoue, M. & Tsugane, S. Green tea consumption and prostate cancer risk in Japanese men: a prospective study. *Am. J. Epidemiol.* **167**, 71–77 (2008).
84. Allen, N. E. *et al.* A prospective study of diet and prostate cancer in Japanese men. *Cancer Causes Control* **15**, 911–920 (2004).
85. Jian, L., Xie, L. P., Lee, A. H. & Binns, C. W. Protective effect of green tea against prostate cancer: a case-control study in southeast China. *Int. J. Cancer* **108**, 130–135 (2004).
86. Sonoda, T. *et al.* A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. *Cancer Sci.* **95**, 238–242 (2004).
87. Bettuzzi, S. *et al.* Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res.* **66**, 1234–1240 (2006).
88. Brausi, M., Rizzi, F. & Bettuzzi, S. Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. *Eur. Urol.* **54**, 472–473 (2008).
89. Jatoi, A. *et al.* A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. *Cancer* **97**, 1442–1446 (2003).
90. Choan, E. *et al.* A prospective clinical trial of green tea for hormone refractory prostate cancer: an evaluation of the complementary/alternative therapy approach. *Urol. Oncol.* **23**, 108–113 (2005).
91. Fleshner, N. *et al.* Randomized trial of Combination Vitamin E, Selenium, and Soy Protein among men with high grade prostatic intraepithelial neoplasia (HGPIN). *J. Urol.* **181**, S263 (2009).
92. Van Patten, C. L., de Boer, J. G. & Tomlinson Guns, E. S. Diet and dietary supplement intervention trials for the prevention of prostate cancer recurrence: a review of the randomized controlled trial evidence. *J. Urol.* **180**, 2314–2321 (2008).
93. Lansky, E. P. & Newman, R. A. *Punica granatum* (pomegranate) and its potential for prevention and treatment of inflammation and cancer. *J. Ethnopharmacol.* **109**, 177–206 (2007).
94. Pantuck, A. J. *et al.* Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin. Cancer Res.* **12**, 4018–4026 (2006).
95. Gann, P. H. Randomized trials of antioxidant supplementation for cancer prevention: first bias, now chance–next, cause. *JAMA* **301**, 102–103 (2009).
96. Lawlor, D. A., Davey Smith, G., Bruckdorfer, K. R., Kundu, D. & Ebrahim, S. Observational versus randomised trial evidence. *Lancet* **364**, 755 (2004).
97. Ornish, D. *et al.* Intensive lifestyle changes may affect the progression of prostate cancer. *J. Urol.* **174**, 1065–1069 (2005).
98. Vaishampayan, U. *et al.* Lycopene and soy isoflavones in the treatment of prostate cancer. *Nutr. Cancer* **59**, 1–7 (2007).
99. Kranse, R. *et al.* Dietary intervention in prostate cancer patients: PSA response in a randomized double-blind placebo-controlled study. *Int. J. Cancer* **113**, 835–840 (2005).
100. Schroder, F. H. *et al.* Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. *Eur. Urol.* **48**, 922–930 (2005).