UNCONVENTIONAL THERAPY FOR PROSTATE CANCER: GOOD, BAD OR QUESTIONABLE?

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Complementary and alternative medicine (CAM) encompasses a wide range of interventions that are often used for the prevention and treatment of malignant disease. As prostate cancer is characterized by strong dietary influences, a long disease latency period and limited treatment strategies for advanced disease, many patients turn to CAM with the belief that they represent a viable therapeutic option that is free of adverse side effects. Although the efficacy of many CAM therapies seems compelling, definitive studies are underway and the potentially harmful effects of these 'natural' interventions need to be recognized.

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The use of CAM for the treatment of malignant disease is common, and a broad array of vitamins, dietary supplements and botanical preparations are used in this context as an alternative to conventional medical treatments. For this discussion, we define conventional medical treatments as those approaches that are widely accepted and practiced by the mainstream Western medical community. Complementary medical therapies are used alongside conventional medicine and examples include aromatherapy, mental imagery and massage. Alternative medical therapies are used in place of conventional medicine and include homeopathic and naturopathic medicine. Clinicians and patients often use the terms 'complementary' and 'alternative' interchangeably. Some agents, particularly vitamins, dietary supplements and botanical preparations are used in both contexts.

Of the many cancers that affect the population, prostate cancer shows several attributes that provide attractive intervention points for the application of CAMs. The disease is extremely common — with more than 220,000 new cases diagnosed annually in the United States alone[1] — and these numbers are projected to increase annually as the ageing population expands. Although specific initiating factors are poorly understood, family history, race and diet are well-documented contributors to risk. Caucasian and African–American men in the United States have a prostate cancer incidence that is 5–50 times greater than that of Japanese men residing in Japan, and the incidence of prostate cancer in Japanese immigrants to the United States is four times that of their native Japanese counterparts. This marked racial and cultural disparity indicates that dietary factors might affect cancer growth. Most prostate cancers initially require the presence of circulating androgens that influence the proliferation and maintenance of the secretory prostate epithelium. Molecular studies also indicate that chronic inflammation might mediate early instigating events in prostate carcinogenesis (BOX 1). Because cell turnover in the prostate is relatively slow, the multistep evolution from an initiated epithelial cell to invasive cancer is estimated to span decades (FIG. 1). This long latency period affords opportunities for intervention with therapies that are designed to delay disease initiation or progression. The standard of care options for treating clinically localized disease include radiation therapies and radical prostatectomy. For advanced disease, ablating androgenic hormones is the mainstay of therapy, and will result in tumour responses in 80–90% of men. Ultimately, however, prostate cancer cells become independent of androgen requirements, and progress to a 'hormone-refractory' state that culminates in

Summary

- The protracted natural history and lack of curative therapy for advanced prostate cancer makes complementary and alternative medicine (CAM) attractive to patients.
- CAM is as widely practiced as traditional medicine.
- Antioxidant and hormonal influences of dietary and alternative therapies hold promise for the prevention and treatment of prostate cancer.
- The lack of quality control of CAMs that are offered as dietary supplements makes them susceptible to adulteration.
- New models for how to incorporate studies of CAM into chemoprevention and therapeutic trials are badly needed.

28,000 deaths per year. The poor response of advanced prostate cancer to any current therapies therefore provides motivation for patients to explore unconventional approaches.

Micronutrients and botanical products have recently been the focus of extensive basic and epidemiological research that is directed towards understanding their potential roles in the prevention and/or treatment of prostatic disease. The results of these studies have led to trials that have been designed to evaluate their clinical efficacy — often with unanticipated results. We will discuss the different classes of micronutrient and botanical preparations that have been evaluated in prostate cancer, and focus on the laboratory, preclinical and clinical studies that involve the most promising and extensively characterized agents. Complicating these studies are issues that concern reproducibility of extraction procedures, botanical mixtures and the presence of adulterants such as those recently identified in the herbal preparation PC-SPES. Although the studies indicate potential benefits for patients with prostate cancer, the pitfalls encountered have ramifications for designing evidence-based clinical trials that are useful for patients and clinicians who make crucial decisions that could affect the quality and length of life.

Box 1 | Inflammation and prostate carcinogenesis

Emerging evidence indicates that inflammation might have a crucial role in the genesis of prostate carcinoma[90]. Sexually transmitted diseases have been associated with a higher risk of prostate carcinoma, either through direct infection of prostate cells or by the indirect effects of the attendant immune-cell inflammatory response[91]. In keeping with this hypothesis, individuals who take anti-inflammatory drugs have a lower rate of prostate cancer diagnoses[92]. Chronic inflammation is often found directly adjacent to proliferative inflammatory atrophy (PIA), a putative precursor to prostate intraepithelial neoplasia (PIN) and prostate cancer (FIG. 1). Immune effector cells produce various oxidants that induce cellular and genomic damage (FIG. 2). De Marzo and colleagues have proposed that recruitment of inflammatory cells and the subsequent production of cytokines and eicosanoids leads to an uncontrolled epithelial regenerative response (manifest as PIA) that, when combined with subsequent additional DNA damage, leads to progression through PIN to frank carcinoma[93].

Antioxidants such as lycopene absorb and dissipate energy from singlet oxygen ($^1O_2$), preventing damage and, potentially, inflammation (FIG. 2). Various compounds, including baicalein and phyto-oestrogens, suppress production of eicosanoids and inflammatory cytokines, potentially blocking the recruitment of additional sources of oxidant damage and, subsequently, prostate carcinogenesis.

Use and rationale for CAM

CAM is defined by the National Center for Complementary and Alternative Medicine (NCCAM) as a group of diverse medical and health-care systems, practices and products that are not normally considered to be conventional medicine[2] (BOX 2). The use of CAM in the United States is both widespread and underappreciated. Anywhere from 30–70% of adult patients with a diagnosis of cancer use some form of CAM and conservative estimates indicate that over 34 billion dollars a year is spent on alternative medicine in the United States[3]. Among patients with prostate cancer, the most commonly used CAM therapies are vitamins (34% of patients), prayer or religious practices (25%) and herbal medicines (13%).

There are many reasons why patients use alternative medical approaches. Ones that are often cited include a distrust or dissatisfaction with conventional medicine, the need for personal control, philosophical congruence (treatments are seen as more compatible with the patients' personal values), the perceived safety of natural products and a search for potential curative therapies when conventional treatments are expected to offer little benefit. Interestingly, most patients do not inform their physician about their use of CAM[4]. For example, in the context of a standard medical history, only 33% of patients with prostate cancer reported their use of complementary medicine, but when questioned specifically, 81% of the patients disclosed their use of CAM[5]. This discrepancy might be due, in part, to fears of physician disapproval, but — more frequently — patients do not think of CAM as a 'medication'.

Despite the extensive use of CAM by patients with prostate cancer, there is relatively little rigorous clinical research to help patients and practitioners decide on the relative merits or drawbacks of different types of interventions. This is, in part, because of the schism that exists in practitioner philosophy. Conventional medicine relies on the statistical analysis of the effects attributed to synthetic compounds or highly purified natural agents in large cohorts of patients who have similar diseases. Many CAM practitioners feel that CAM — by its very nature — must be tailored to the individual patient and is therefore not appropriate for large-scale randomized studies. Despite these limitations, there are provocative epidemiological studies and an extensive amount of basic research that supports the potential role for therapies that are presently considered to be alternative or complementary in the prevention and treatment of prostate cancer.

Vitamins and minerals

The epidemiology of prostate carcinoma indicates that environmental factors appreciably influence the development and progression of neoplastic disease (FIG. 1). One of the main focuses of study has centred on the

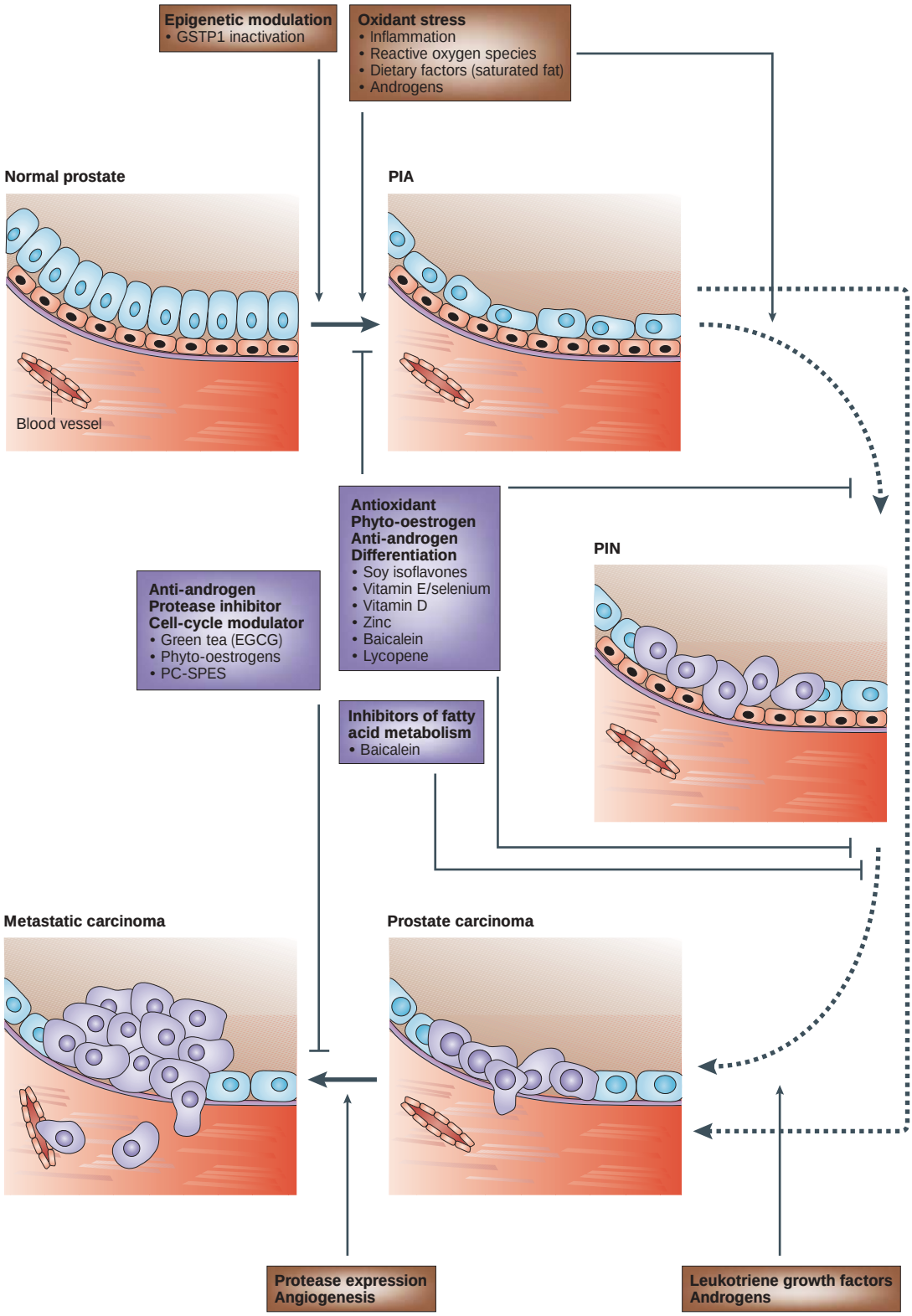


Figure 1 | **Prostate carcinogenesis and potential intervention points for nutrient and botanical agents**. As with many epithelial malignancies, prostate carcinoma is thought to arise as a multistep process with progression stages that include precancerous lesions defined as proliferative inflammatory atrophy (PIA) and prostate intraepithelial neoplasia (PIN). The development of carcinoma is followed by locally invasive disease and the subsequent dissemination of tumour cells to distant sites. To facilitate these events, molecular alterations in the tumour cell and host environment occur that mediate specific biochemical processes such as androgen-independent growth and angiogenesis (brown boxes). Nutrient and botanical compounds have been shown to modulate several of these crucial biochemical reactions, and so might alter the progression rates of prostate neoplasia (purple boxes). GSTP1, glutathione *S*-transferase P1.

Box 2 | Types of CAM

- Aromatherapy
- Biofeedback
- Chiropractic treatment
- Dietary intervention
- Energy healing
- Folk remedy
- Herbal and biological agents
- Hypnosis
- Imagery
- Magnets
- Massage
- Naturopathy
- Osteopathy
- Mind–body therapies
- Relaxation
- Spiritual healing/religion
- Vitamin supplements
- Yoga

identification of dietary factors — such as vitamins and trace elements — that could promote or inhibit carcinogenesis[6]. The suggestion that specific chemical compounds in food might influence cancer growth has led to their use both for preventive and therapeutic effect (TABLE 1,2). Although the epidemiological and biochemical data for several compounds are compelling, definitive recommendations await the completion of large randomized clinical trials.

Vitamins are organic compounds that humans cannot synthesize and must ingest to prevent disorders of metabolism[7]. Numerous population-based observational and interventional trials have sought to determine the influence of specific vitamins on prostate carcinogenesis. The interpretation of these studies is not straightforward, in part because of the complexity and variability of the human diet as well as genetic variation within populations that influence metabolic pathways. However, several reports strongly indicate associations between particular food constituents and prostate cancer. Increasingly sophisticated biochemical studies indicate molecular mechanisms that support antineoplastic effects. Among the many compounds assessed, selenium and vitamins A, C, D and E, seem to have potential preventive or therapeutic benefit in some studies, though direct causal associations have yet to be proven. Despite the absence of convincing evidence, vitamin and mineral supplements are used extensively by patients that have been diagnosed with prostate cancer[5,8] with the belief that such supplements might actually prevent or treat disease, and at least will not cause harm.

Retinoids and vitamin A. Retinoids are a class of compounds that include natural forms of vitamin A — retinol, retinyl esters, retinal and retinoic acid — as well as their synthetic derivatives. Retinol and retinal are found in high concentrations in foods such as liver and fish oils[7]. Retinoic acid is the active metabolite that is produced by the endogenous dietary oxidation of retinol and its esters, and is not found in appreciable concentrations in any natural source. Retinoids show antiproliferative activities, in part, through the induction of cellular differentiation and apoptotic responses[9]. One case–control study — comparing the diets of 207 men with histologically confirmed prostate cancer and 207 randomly selected men — showed that higher dietary retinol intake was associated with a reduced risk of prostate cancer[10]. However, a conflicting study showed an increased risk of prostate cancer in men aged greater than 70 in the quartile with the highest, relative to the lowest, intake, and a prospective cohort study of 58,279 men found no association with retinol intake and prostate cancer risk[11]. So, although synthetic retinoids such as fenretinide show substantial antiproliferative effects on prostate cells in model systems, it seems that dietary vitamin A exerts minimal effects in humans. This might be because of feedback control mechanisms that limit retinoid stores in the body or the inability to achieve effective tissue levels because of toxicities that occur with high-dose vitamin A supplementation[12].

Vitamin C. Ascorbic acid (vitamin C) — found widely in both animal- and plant-derived foods — has a crucial role in diverse cellular processes. These include the scavenging of free radicals that are generated as by-products of metabolism, the synthesis of collagen and hormones, haemostasis, and the protection of lipid membranes[7]. Interestingly, vitamin C has also been shown to inhibit tumour-cell growth and viability *in vitro* through various mechanisms, including cell-cycle arrest, inhibition of DNA synthesis and reduction of intracellular levels of chemically reactive sulphydryls (reviewed in REF. 13). Despite provocative results from animal studies that show antitumour effects of vitamin C or combinations of vitamin C and vitamin K[13], most epidemiological studies have not shown a convincing association that links either increased vitamin C intake or serum levels with a reduction in prostate cancer incidence[14,15]. However, most studies have not investigated whether a trend in dose-response exists for the effect of vitamin C against prostate cancer[16].

Vitamin D. Vitamin D3 (1,25 dihydroxyvitamin D3; calcitriol) is produced by the action of ultraviolet (UV) light on precursor molecules in skin cells. So, plasma vitamin D levels vary with seasonal sunlight, lifestyles and geographic location. Vitamin D is also present in the diet, found in high levels in certain fish species, eggs and fortified dairy products. It modulates calcium and phosphate homeostasis and has also been shown to influence cellular growth and differentiation[17]. The hypothesis that vitamin D deficiency might be causally related to prostate carcinogenesis was developed from observations that northern latitudes and, presumably, less sun exposure, all positively correlate with increased prostate cancer risk[18]. Indeed, numerous *in vitro* studies show the consistent growth-inhibitory effects and

Table 1 | Observational studies of dietary and nutritional compounds on prostate cancer incidence

Class	Compound	Sources*	Proposed mechanism(s)	Association with level of dietary intake	References
Vitamins					
	Vitamin A/retinoids	Liver, fish oils	Differentiation/apoptosis	No association High = reduced risk (compared with low) High = increased risk (compared with low)	94 10 95
	Vitamin D	Sunlight, fish, dairy	Differentiation/cell-cycle modulation	No association	96
	Vitamin E	Nuts, seeds, oils	Antioxidant/interactions with AR	No association High = reduced risk (compared with low)	94 26
	Vitamin C	Fruits	Antioxidant/others‡	No association	94
Minerals					
	Calcium	Dairy products	Modulation of vitamin-D levels	High = increased risk (compared with low) No association High = increased risk (compared with low)	43 16 97
	Selenium	Meat, fish, grains	Antioxidant/apoptosis/ cell-cycle modulation§	No association High = reduced risk (compared with low)	98 99
	Zinc	Meat, legumes, dairy	Antioxidant/membrane stabilizer/enzyme cofactor	No association High = reduced risk (compared with low)	98 100
Phytochemicals					
	β-Carotenes	Fruits, vegetables	Antioxidant	Low = increased risk (compared with high) Low = increased risk (compared to high) Low levels = 45% increased risk of PRCA	101 102 14
	Genistein	Soy products	Oestrogenic/kinase and topoisomerase inhibition	High intake = lower PRCA risk	
	Diadzein	Soy products	Oestrogenic/kinase and topoisomerase inhibition	High intake = lower PRCA risk	103
	Polyphenolics	Black and green tea	Antioxidant/MMP inhibition/cell-cycle modulation	High intake = lower PRCA risk No association	45 104
	Lycopene	Tomatoes	Antioxidant/cell-cycle modulation	High = reduced risk (compared with low)	31

*Partial listing of the food sources of various vitamins, minerals and phytochemicals. ‡Mechanisms proposed in REFS 6,12. §Mechanisms proposed in REFS 36,38. AR, androgen receptor MMP, matrix metalloproteinase; OR, odds ratio; PRCA, prostate carcinoma.

induction of differentiation of prostate carcinoma cells by vitamin D, and animal studies show that vitamin D not only reduces the incidence of prostate cancer but also suppresses metastases[19,20]. Interestingly, one of the most active regimens for the treatment of advanced prostate cancer involves the combination of high-dose vitamin D with the chemotherapeutic agent docetaxel, with response rates of 80%[21]. However, several large population-based studies that measured vitamin D intake or serum levels in humans have not provided compelling data to support a protective effect of vitamin D towards prostate carcinogenesis (reviewed in REF. 22). It is possible that measures of vitamin D metabolites, binding proteins, genetic polymorphisms in metabolic enzymes or receptors, or serial measurements of levels over time could yield more consistent associations, but so far these data do not support a role for vitamin D supplementation as an approach for prostate cancer risk reduction in the general population.

Vitamin E. The vitamin E designation includes α-, β-, γ- and δ-tocopherol, and the TOCOTRIENOLS. Of these, α-tocopherol is the form that is present in dietary supplements, though γ-tocopherol is the most prominent in the human diet, and possesses robust antioxidant function[23]. Numerous studies have shown potent antioxidant effects of vitamin E and the suppression of cancer growth *in vitro* and in model systems[15,24]. Vitamin E succinate can induce apoptosis in the LNCaP prostate cancer cell line, and has recently been shown to inhibit the expression of the androgen receptor — a crucial mediator of prostate-cell growth[25]. Until recently, epidemiological data supporting a role for vitamin E in prostate carcinogenesis was not particularly persuasive, as most cohort and case–control studies have found no association for dietary or supplemental vitamin E intake and prostate carcinoma (reviewed in REF. 26). However, three recent case–control studies showed marked inverse correlations between dietary vitamin E and

TOCOPHEROLS AND TOCOTRIENOLS
Tocopherols are substituted benzopyranols (methyl tocols) that occur in vegetable oils. Different forms (α, β, γ and δ) are recognized according to the number or position of methyl groups on the aromatic ring. α-tocopherol is an important natural antioxidant. Tocotrienols have similar ring structures as tocopherols, but have three double bonds in the aliphatic chain.

Table 2 | Selected intervention trials of CAM*

Class	Compound	Type of study	Aim of study	Result	References
Vitamins					
	Vitamin E	Phase III	Prevention of lung cancer in smokers	PRCA reduction‡	29
		Phase III	Prevention of PRCA	Ongoing	34
Minerals					
	Selenium	Phase III	Prevention of skin cancer	PRCA reduction	36
		Phase III	Prevention of PRCA	Ongoing	34
Phytochemicals					
	Soy Products	Phase I	Treatment of advanced PRCA	No PRCA response; no toxicity	105
		Phase II	Treatment of HSPC and HRPC	No PRCA response; no toxicity	55
	Lycopene	Neoadjuvant	Treatment of localized PRCA	Reduction in prostate oxidative damage (28%) and PSA (17.5%)	69
		Neoadjuvant	Treatment of localized PRCA	Reduction in positive margins, tumour volume and diffuse PIN	70
	β-Carotene	Phase III	Prevention of cancer and cardiovascular disease	No influence on overall PRCA incidence	106
		Phase III	Prevention of lung cancer in smokers	PRCA increase	29
	Green tea	Phase II	Treatment of HRPC	No PSA responses; grade 3–4 toxicity noted	51
	PC-SPES	Phase II	Treatment of metastatic PRCA	PSA reduction in 100% HSPC and 54% HRPC	79
		Phase III	Treatment with PC-SPES versus DES in HRPC	PSA reduction in 45%§	80

*For further information, see the ClinicalTrials web site in the online links box. ‡Secondary end point. §Terminated early due to identification of contaminants in lots of PC-SPES. CAM, complementary and alternative medicine; DES, diethylstilbestrol; HRPC, hormone-refractory prostate cancer; HSPC, hormone-sensitive prostate cancer; PIN, prostate intraepithelial neoplasia; PRCA, prostate carcinoma; PSA, prostate-specific antigen.

prostate cancer risk of 40% or greater[26–28] (TABLE 1). These findings are supported by data reported in the α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC), in which >29,000 male smokers were randomized to determine if supplements of vitamin A and/or β-carotene would reduce the incidence of lung cancer[29] (TABLE 2). Although an increased risk of lung cancer was observed, the results showed a 32% reduction in the incidence of prostate cancer in those men receiving vitamin E and a 41% decrease in mortality.

These numbers are striking, but it is possible that the benefits of vitamin E primarily affect smokers, and will not influence the development or progression of prostate cancer in non-smokers[30]. Support for this hypothesis comes from the prospective Physicians Health Study, which found that smokers with the highest levels of α-tocopherol had a risk reduction of almost 50% for developing aggressive prostate cancer in contrast to non-smokers who did not show reduced cancer incidence[31]. The United States Health Professionals' Follow-up Study also found that there was no association between vitamin E intake and prostate cancer in non-smokers and, indeed, those non-smokers who were taking in the highest amounts of vitamin E supplements (>100 IU/day) actually had an increased risk of advanced prostate cancer[32]. But among smokers, the daily ingestion of >100 IU of vitamin E supplements produced a 56% risk reduction in lethal or advanced prostate cancer relative to non-users. Although the risks of taking vitamin E are generally low, taking vitamin E with aspirin led to a greater incidence of oral bleeding compared with those on aspirin alone[33] and men taking vitamin E had a non-statistically significant increased risk of haemorrhagic stroke. Overall, the association between vitamin E and prostate cancer was compelling enough to initiate the Selenium and Vitamin E Chemoprevention Trial (SELECT) that aims to determine if vitamin E and/or selenium supplementation will reduce prostate carcinogenesis[34] (discussed below; TABLE 2). One potential concern regarding the study design involves the planned doses of vitamin E, which are fourfold greater than those used in the ATBC study.

Selenium. Selenium — a trace element that is essential for life — is found in many foods, including meat, fish, eggs, dairy products and grains. Selenium concentrations in these foods are primarily dependent on the soil content in the region producing the food[35]. The recommended daily allowance for selenium is 70 μg/day for men, and selenium supplements are available that contain 50–200 μg of selenium in its organic form (for example, yeast or selenomethionine). Epidemiological studies using various designs generally support an

inverse correlation between selenium intake and prostate incidence and mortality (reviewed in REF. 37). This conclusion gained strong support from the secondary analysis of data derived from the Nutritional Prevention of Cancer Study, a randomized trial of selenium supplementation for the prevention of non-melanoma skin cancer recurrence[36]. Patients in this trial who received 200 μg/day of selenium had a remarkable 65% reduction in the incidence of prostate cancer. The beneficial effect was primarily seen in men who had medium to low selenium serum levels at the beginning of the study. However, potentially confounding factors in the study include examining the incidence of prostate cancer as a secondary, not a primary, endpoint and the higher than expected rates of several cancers in the cohort enrolled for study[30].

Selenium has been shown to inhibit experimental carcinogenesis by various mechanisms[37,38]. Beneficial effects of selenium have been thought to primarily involve protection from oxidative stress through the action of selenium-containing enzymes such as glutathione peroxidase[39]. However, recent studies evaluating changes in cellular gene expression resulting from selenium exposure show that a multitude of genes seem to be selenium-responsive, including cell-cycle regulators, mediators of apoptosis and modulators of DNA repair[40]. These findings indicate that selenium could prevent cancer at an early stage, but promote it at a later stage.

Together, conclusions from the epidemiological and laboratory studies indicate that selenium exerts a modest to moderate beneficial effect. However, it remains to be determined if this effect is seen only in those individuals with low selenium levels, or if the benefit extends to all men at risk for prostate cancer. This is of particular importance as selenium is not a benign compound. An update from the Nutritional Prevention of Cancer Study found that men with the highest initial serum selenium levels had an increase in cancer risk with selenium supplementation[41]. In addition, selenium toxicity can produce gastrointestinal problems, nail-bed changes, hair loss, fatigue and neurological disorders[42]. Data indicating the potential benefit of selenium supplements — along with data regarding vitamin E supplementation — generated enough enthusiasm to launch the randomized SELECT study[34]. The experimental design for this study of 32,000 men consists of 4 regimens: selenium 200 μg/day, vitamin E 400 mg/day, selenium and vitamin E, and a placebo. On completion in 7–12 years, this trial should best determine the role of selenium in the prevention, and possibly the progression, of prostate cancer. Until that time, the use of selenium and vitamin E supplements should be viewed with caution.

Calcium. Calcium levels in the body are tightly regulated by parathyroid hormone and vitamin D. As high dietary calcium intake can suppress serum vitamin D levels, measuring calcium intake has been viewed as an additional approach for evaluating the influence of vitamin D on prostate carcinogenesis[22]. Several epidemiological studies have evaluated the potential association between calcium intake and prostate cancer risk, with conflicting results. Three case–control studies and one cohort study have reported no association, whereas one case–control and two cohort studies reported positive associations (reviewed in REF. 22). For example, data from the Health Professionals Follow-up Study indicate that men who consume more than 2,000 mg of calcium per day had a 4.6-fold increased risk for metastatic or fatal prostate cancer compared with those individuals consuming less than 500 mg of calcium per day[43]. By contrast, a large case–control study of 697 individuals found no correlation with calcium supplementation and prostate cancer[16]. Potentially confounding dietary variables affect these studies, including total energy intake and factors that influence vitamin D levels, such as phosphorous and fructose. The Baltimore Longitudinal Health Study — which evaluated calcium as a risk factor for prostate cancer and paid specific attention to these other variables — did not identify an associated prostate cancer risk[44]. As with vitamin D, polymorphisms in the vitamin D receptor and/or other metabolic enzymes, heterogeneity in prostate cancer itself, or additional unrecognized modifying dietary constituents could influence these results. So, low calcium levels and calcium intake supplemented to the recommended daily levels of 800–1,200 mg are not associated with an increased risk of prostate cancer. However, supplementing the diet with excess calcium could increase incidence or influence disease progression.

Herbal compounds and derivatives

Asian diets and Chinese medical therapies incorporate an extensive array of plant-derived foods, herbs and herbal extracts that contain numerous POLYPHENOLIC COMPOUNDS. It is hypothesized that these compounds contribute to the lower incidence of prostate cancer in Asians relative to Caucasians and African–Americans. Polyphenols are characterized by their diaryl nucleus and, with over 8,000 distinct compounds defined so far, this group can be subdivided into flavones, flavonoids, isoflavones and tannins. Many isoflavones are also PHYTO-OESTROGENS that bind to oestrogen receptors and elicit oestrogenic effects in target tissues. Four products in particular — green tea, *Scutellaria baicalensis*, soy and lycopenes — are notably rich in polyphenols and have been studied in the context of prostate carcinoma.

Green tea. Green tea is a popular beverage in many Asian societies and some studies indicate a lower incidence of prostate carcinoma in heavy tea drinkers[45]. Green tea contains various flavonoid polyphenols, which have been tested *in vitro* and *in vivo* for effects on prostate carcinogenesis. Most studies have evaluated green-tea preparations that contain at least four active polyphenolic compounds including epicatechin, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate (EGCG). In bioassays, EGCG comprises 10–60% of the polyphenol constituents in green-tea infusions and has been shown to arrest LNCaP and DU145 prostate cancer cells at G0–G1 of the cell cycle. EGCG activity is mediated through the modulation of

POLYPHENOLS
Chemicals that contain more than one aromatic phenol ring.

PHYTO-OESTROGENS
Chemicals that are derived from plant sources which have oestrogen-like effects on animal tissues or cell lines.

cell-cycle regulators, and can also induce apoptosis[46]. EGCG also inhibits METALLOPROTEINASES *in vitro*, although this effect is achieved at concentrations that are markedly higher than the physiological levels achieved in humans[47]. EGCG is also an antioxidant and effectively prevents lipid peroxidation and DNA damage in tumour lines other than prostate cancer.

Exciting preclinical data on the use of green tea for chemoprevention were generated using the transgenic adenocarcinoma mouse protocol (TRAMP) model; a line of mice that have been genetically engineered to develop prostate adenocarcinoma. In this study, green-tea preparations were administered orally to TRAMP MICE for 24 weeks, achieving a 40% reduction in localized tumour development at 20 and 30 weeks. Administration also completely suppressed metastatic spread to lymph nodes, liver, lungs and bone, and improved survival by 70% compared with control animals[48]. In the androgen-dependent LNCaP orthotopic model of prostate cancer, Zhou *et al.* showed that administration of green tea, black tea or soy phytochemical extract effectively suppressed tumour growth following implantation, and inhibited the development of lymph-node metastasis. Interestingly, green tea alone did not substantially affect final tumour growth, although the combination of green tea and soy phytochemicals did decrease tumour size, prostate-specific antigen (PSA) and serum testosterone levels[49].

A Phase I study of green-tea extract in the treatment of patients with various tumours recently reported no significant responses using the maximally tolerated oral dose of 1 g/m^2 three times a day, although 10 of 49 patients had stable disease for six months or longer[50]. In a Phase II study — in which 6 g/day of tea was administered to 42 patients with asymptomatic, androgen-independent prostate cancer[51] — a single patient achieved a PSA response of >50% that lasted for approximately one month. Patients suffered marked toxicities in this study, most notably diarrhoea, nausea and fatigue. From these studies, investigators concluded that green tea has minimal antineoplastic activity against androgen-independent prostate cancer.

Soy isoflavones. The principal isoflavones in soy include genistein, daidzein and biochanin A, which occur naturally as glucosidic conjugates and are metabolized to their active forms in the gut. Soy products have a particularly broad range of mechanisms for chemopreventive and antineoplastic activities. Their weak phytoestrogenic effects include differentiation, protection from DNA damage and modulation of hormones. Soy isoflavones inhibit 5α-reductase, the enzyme that is responsible for the conversion of testosterone to the more potent androgen dihydrotestosterone[52]. Genistein also inhibits various tyrosine kinases, as well as DNA topoisomerases[53]. Administration of genistein to TRAMP mice for 25 weeks suppressed the development of a histologically defined subset of aggressive prostate tumours in a dose-dependent fashion, however, the absolute rate of tumour development was unaffected[54]. In a Phase II study, patients with androgen dependent (n=21) or androgen independent (n=20) prostate cancer were treated with a daidzein/genistein preparation for 3–6 months. Treatment was well tolerated, but there was no reduction in PSA and no other evidence of response[55]. Several randomized studies of soy isoflavones as chemopreventive agents are ongoing and the results are eagerly awaited.

Scutellaria baicalensis. The herb *Scutellaria baicalensis georgi* — also known as baical, Chinese skullcap, golden root or Huang qin — has been used extensively in traditional Chinese medicine for various therapeutic indications. *Scutellaria* contains very high levels of flavonoids, including baicalin — a flavone glycoside that is metabolized in the gut by intestinal microflora to baicalein (which is also present at lower concentrations in *Scutellaria*). Baicalein inhibits enzymatic synthesis of EICOSANOIDS, which are important mediators of inflammation and prostate tumour cell proliferation. Baicalein impairs the proliferation of androgen-independent PC-3 and DU145 prostate cancer cell lines, and induces cell-cycle arrest at G0–G1 and apoptosis at concentrations achieved in humans. Administration of the eicosanoid 12-hydroxyeicosatetraenoic acid, the product of 12-lipoxygenase, rescued baicalein-treated cells, indicating that the ability of baicalein to inhibit 12-lipoxygenase was responsible for its antineoplastic activities[56]. Similar effects on cell cycle and cell proliferation were shown in androgen-sensitive LNCaP cells with an additional finding that, at clinically achievable concentrations, baicalein markedly suppressed the expression of the androgen receptor[57].

Preclinical data for the efficacy of *Scutellaria* or baicalein in prostate cancer models is limited to a single report in which DU145 prostate cancer cells were pretreated with baicalein and other agents before the injection of tumour cells into tail veins of SCID MICE. The number of lung metastases were decreased 20% by baicalein pretreatment[58]. *Scutellaria* also contains other flavonoids, including neobaicalein, wogonin and wogonoside, which have substantial cytotoxic activity against various cancer types *in vitro*[59]. Although clinical trials with *Scutellaria baicalensis* or baicalein have not been reported, both were components of a herbal mixture — PC-SPES — which is used to treat prostate carcinoma. Analysis of baicalin in different batches of PC-SPES showed that concentrations of the parental glycoside were as high as 39 mg/g of PC-SPES, indicating that patients have taken 76–130 mg/day of baicalin safely[60]. The contribution of the baicalin component of PC-SPES relative to the overall efficacy of the herbal mixture has not been determined.

Lycopene. Compelling epidemiological studies have shown a decreased risk of prostate cancer with two or more servings of raw and cooked tomato products[61–63]. Tomatoes contain various compounds that have chemopreventive and antineoplastic effects, including CAROTENOIDS, polyphenols and vitamins. Carotenoids are

METALLOPROTEINASES
Proteolytic enzymes that break down the extracellular matrix.

TRAMP MICE
(Transgenic adenocarcinoma of the mouse prostate). A transgenic mouse strain in which the oncogenic SV40 T antigen is expressed in prostate tissue. Animals spontaneously develop preneoplastic lesions and malignancy of the prostate and the model has been used to study methods to prevent and treat prostate cancer *in vivo*.

PSA
(Prostate-specific antigen). A member of the kallikrein family that is made by normal and malignant prostate tissues and that can be secreted into the blood. Detection of PSA from blood tests is one way of detecting and following prostate cancer.

EICOSANOIDS
A class of hormone-like substances that are formed in the body from long-chain essential fatty acids.

SCID MICE
Mice that are homozygous for the SCID mutation have compromised B- and T-cell immunity. This lack of immunity means that they can support human tumour xenografts for preclinical studies.

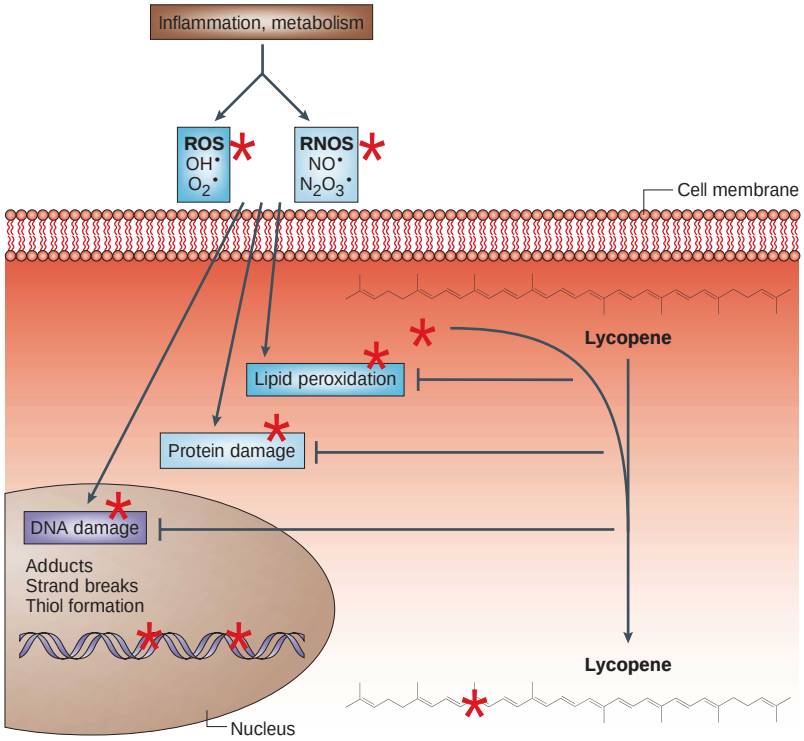


Figure 2 | **Antioxidant effect of carotenoids: scavenging of reactive oxygen species and prevention of cellular damage.** Processes involved in metabolism and inflammation produce free radicals in the form of reactive oxygen species (ROS) and reactive nitric-oxide species (RNOS). These reactive intermediates can modify and damage lipids, proteins and DNA resulting in the disruption of key cellular processes such as DNA repair, cell-cycle checkpoints and apoptosis. Antioxidants such as lycopene can serve to absorb or scavenge the excitation energy (indicated by red asterisk) from free radicals where the excess energy is dissipated though rotational and vibrational interactions between lycopene and solvent, thereby protecting crucial cellular molecules from damage.

extremely effective antioxidants and lycopene is the predominant carotenoid in tomatoes, making up 90% of carotenoids in most products. Because there are few other sources of lycopene in the Western diet, the association of decreased prostate cancer risk and tomato-product intake has led to the specific focus on lycopene, although most studies use mixtures of tomato products rather than purified lycopene. Gann *et al.* prospectively analysed levels of five carotenoids contained in tomato products as well as retinol, α- and γ-tocopherol in men participating in the Physicians' Health Study[31]. Lycopene was the only carotenoid that showed a significant association with risk for prostate cancer, confirming an inverse relationship between plasma lycopene levels and prostate cancer. However, not all studies have shown a clear association between tomato intake and prostate cancer risk, and the relative benefit of lycopene-containing products remains controversial[64].

Lycopene is the most efficient antioxidant among the natural carotenoids and scavenges peroxyl free radicals and other REACTIVE OXYGEN SPECIES, protecting cells against damage to DNA, proteins, carbohydrates and lipids[65,66] (FIG 2). The proposed mechanism of lycopene chemoprevention is through suppression of lipid peroxidation, generation of free radicals and, ultimately, a decrease in DNA damage. Lycopene also inhibits cell-cycle progression in breast and endometrial carcinoma, potentially through suppression of cyclin D levels[67]. Few preclinical studies addressing the effects of lycopene and lycopene-rich diets on prostate carcinogenesis have been reported. Those that exist have been carried out in an attempt to prevent chemical carcinogenesis and have not shown significant effects on prostate cancer incidence[68].

Chen *et al.* carried out a prospective study of the effect of tomato-based products on lycopene levels and measures of oxidative damage in patients undergoing prostatectomy for localized prostate cancer[69]. Three weeks of dietary intervention doubled serum levels and tripled prostate levels of lycopene compared with controls. Measures of oxidative damage in lymphocytes from these patients were diminished after dietary intervention compared with pretreatment levels, and prostate tissue in treated patients revealed decreased levels of oxidative damage. Intriguingly, PSA levels also decreased during the study.

A similar randomized study was carried out using OLEORESIN extract containing the equivalent of 30 mg/day of lycopene for three weeks that was administered before radical prostatectomy[70]. The authors reported that tumour volume was significantly decreased in the patients receiving dietary intervention. In addition, lycopene intake reduced the residual tumour left in the surgical bed after prostatectomy. Prostate and serum levels of lycopene were similar in the two groups and changes in PSA levels were not statistically different. This reported difference in pathological features will require confirmation in a larger cohort of patients. Randomized trials to assess the efficacy of lycopene in primary chemoprevention are ongoing and it remains an open question as to whether lycopene itself is effective, or whether more complex food extracts are required.

The cautionary tale of PC-SPES

For many of the same reasons that draw patients to use specific individual herbal compounds and their derivatives, such as those discussed above, mixtures of these botanical substances are extremely popular for their proposed preventive and therapeutic effects. The additional rationale justifying combination therapies are the potential for synergistic activity and the ability to 'buffer' the toxic effects of any single constituent[71,72]. Conventional chemotherapeutic regimens embrace a similar strategy, but are based on extensive knowledge of specific biochemical reactions that target destruction of cancer cells . The quality control of complex botanical preparations involves important additional challenges, as exemplified by the recent tempest surrounding the herbal preparation PC-SPES.

Sales of PC-SPES as a dietary supplement for 'prostate health' began in 1996 — the name PC-SPES being derived from 'prostate cancer' (PC) and 'spes', the Latin word for hope. This botanical mixture was used primarily by patients for the treatment of prostate carcinoma, as the formulation comprised extracts of eight herbs —

CAROTENOIDS
Any group of pigments, yellow to deep red in colour, chemically consisting of polyisoprene hydrocarbons. Carotenoids are synthesized by higher plants and concentrate in animal fat when eaten.

REACTIVE OXYGEN SPECIES
The chemical reactions and physical changes involving molecular oxygen (O_2), or any of the reactive oxygen species such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals (^-OH).

OLEORESIN
A mixture of oil and resin that occurs naturally in certain plant tissues, and that can be extracted.

Ganoderma lucidum, *Scutellaria baicalensis*, *Rabdosia rubescens*, *Isatis indigotica*, *Dendranthema morifolium*, *Serenoa repens*, *Panax notoginseng* and *Glycyrrhiza uralensis* — that were selected based either on their use in Chinese medicinal therapy for urinary problems, or their antitumour efficacy against cancer cell lines[71,73]. In accordance with traditional Chinese medical practice, the herbs comprise four attributes to achieve synergy: active principles (such as *Scutellaria*), adjuvants (for example, *Ganoderma*), correctives (for example, *Dendranthema*), and flavours (for example, *Glycyrrhiza*)[71]. *Serenoa repens*, also known as SAW PALMETTO, has been shown to relieve urinary obstructive symptoms due to benign prostatic hypertrophy[74,75]. Although studies that document the effects of *Serenoa repens* on prostate carcinoma in patients are lacking, *in vitro* experiments indicate anticancer activity[76]. PC-SPES was reportedly standardized by chemical analysis and the measurements of key active components (for example, baicalin and oridonin) were assessed by HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY to ensure batch-to-batch consistency[71]. Extrapolation from the known chemical complexities of the individual herbs that are used to formulate PC-SPES indicates that the extract comprises hundreds to thousands of distinct chemical compounds that include isoflavones, terpenes, oligosugars, saponins and alkaloids.

More than 45 laboratory and clinical studies have been published that describe the effects and mechanisms of PC-SPES activity[72]. These include demonstrations of cytostatic and cytotoxic activity *in vitro*, inhibition of tumour growth in animals, and specific mechanistic studies showing modulation of androgen-receptor expression, apoptosis and microtubule synthesis. Clinical studies consistently reported the effectiveness of PC-SPES in reducing prostate tumour growth in both androgen-dependent and androgen-independent disease, determined using reductions in PSA levels as a surrogate marker of tumour growth[77–79]. The side effects that were reported by patients taking PC-SPES included breast enlargement and deep vein thrombosis; indicating that one mechanism mediating antitumour activity was through oestrogenic constituents. Indeed, laboratory studies showed strong oestrogenic effects, although early studies did not identify known oestrogens in the PC-SPES formulation[77]. The exciting clinical responses combined with basic scientific studies indicating anticancer activity prompted the support of four PC-SPES clinical trials by the NCCAM and a randomized study sponsored by the Association for the Cure of Cancer of the Prostate that directly compared PC-SPES against the synthetic oestrogen diethylstilbestrol (DES) in men with advanced prostate cancer[80,81].

Questions regarding specific mechanisms of action, variability in PC-SPES preparations, oestrogenic side effects and case reports of various other complications such as haemorrhagic episodes[82] prompted further investigations into the chemical make-up of PC-SPES. In a rapid succession of events, these studies identified several synthetic compounds that are present in varying amounts in different batches of PC-SPES, including DES, the anticoagulant warfarin and the anti-inflammatory indomethacin[60]. So far, the source of these additives has not been determined. The benzodiazepine alprazolam was identified in SPES, another herbal supplement also produced by BotanicLab, the manufacturer of PC-SPES[81]. The presence of these drugs prompted the California Department of Health Services and, subsequently, the Food and Drug Administration (FDA) to issue warnings describing the adulteration of PC-SPES. The product was recalled by BotanicLab, production was subsequently stopped and the company ceased business operations. Studies supported by NCCAM were put on hold, and the Phase II multicentre randomized trial of PC-SPES and diethylstilbestrol (DES) was halted.

Interestingly, preliminary results from this trial indicated improved outcomes for those patients on the PC-SPES arm (47% response rate) compared with DES (28% response rate)[80]. The laboratory studies clearly indicate many intriguing mechanisms of cytotoxic activity, and the clinical studies support a role for PC-SPES in patients with advanced, hormone-refractory disease: a patient population without many effective conventional therapeutic options. So, although the therapeutic application of PC-SPES was promising, a lingering question remains —did PC-SPES contain other synthetic compounds that were simply not identified? At present, PC-SPES is not available for purchase in the United States, though several products advertising similar herbal extract components — PC-Plus, PC-Care — have been produced and marketed. No research studies demonstrating the *in vitro* or clinical efficacy of these mixtures have been published.

Clinical efficacy of CAM

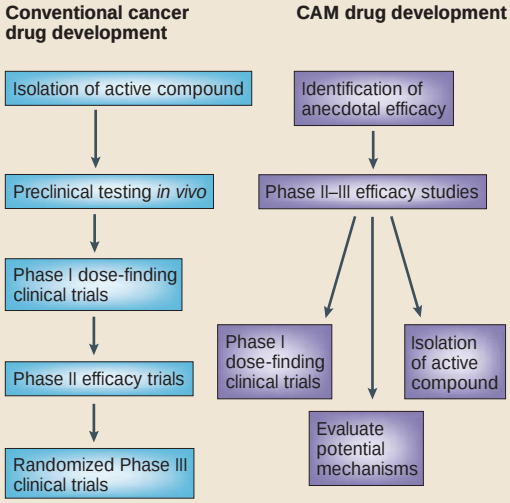
There are many unresolved issues concerning the optimal approach for studying promising complex botanical preparations, and many lessons to be learned when considering how to approach rigorous analyses of formulation and efficacy of these potentially therapeutic mixtures.

The first issue, which is perhaps most relevant to the problems that arose with the use of PC-SPES, is the question of safety and standardization of dietary supplements such as complex herbal preparations. The Dietary Supplement Health and Education Act (DSHEA) was enacted in the United States in 1994 to improve public access to dietary supplements. Herbal products that do not claim to diagnose, treat, cure or prevent a specific disease are considered dietary supplements. Because PC-SPES was considered a dietary supplement, Good Manufacturing Practices, which are designed to assure quality and standardization of a product, were not required. In addition, under DSHEA, dietary supplements are not subject to FDA assessment of safety and toxicity before marketing, so the primary responsibility falls to the manufacturer to establish and monitor safety. This meant that little scientific information was required or is, even now, available regarding formulation, standardization, safety, efficacy, contra-indications, interactions and appropriate use of PC-SPES.

SAW-PALMETTO
A small berry-shaped fruit that grows on the Saw palmetto palm tree (known as sabal in Europe). Saw palmetto grows naturally in the southeast United States (for example, in Georgia, Mississippi and Florida) and has been used for thousands of years by the Native Americans to treat urinary problems.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY
A method that is used to separate molecules through the use of high-pressure application of complex solutions to matrices that preferentially bind or exclude species depending on the matrix and the compound of interest.

Box 3 | Drug development pathways: conventional and alternative approaches



The Drug Development Program at the National Cancer Institute has been the model for identification of new cancer therapeutics for the past 50 years. Originally, a bioassay for activity is developed and used for high-throughput analysis of candidate compounds. Extracts of agents of interest are obtained and tested *in vitro* for selective cytotoxicity against panels of cancer cell lines. Active extracts are fractionated, and purification and testing is continued until a pure component is isolated (blue boxes in figure). Then, *in vitro* and preclinical studies are performed to define mechanisms of action and levels of safety for clinical studies in patients with malignancy. Phase I studies are designed to define the maximally tolerated dose and dosing interval of a compound in patients with advanced malignancy. The compound is then used to treat patients with a defined stage and type of cancer, often identified by the Phase I studies. If Phase II activity is promising, Phase II/III randomized studies will then be carried out, comparing current therapies with the combination of interest. Other groups have used different assay systems to screen for activity, including inhibition of enzymes such as kinases. Advances in genomics and proteomics might soon allow high-throughput analyses of molecular signatures for tumour cells of interest and their response to model agents. Matching a given molecular signature for damage or apoptosis to a screen of candidate compounds might be technically and financially feasible and might be preferable in that it allows concurrent analysis of potential mechanisms of cytotoxicity.

By contrast, CAM trials progress and work in the opposite direction (purple boxes in figure). They start by identifying agents with anecdotal efficacy and a history of safe use by the general public. If the application for a trial addresses an important public health issue that has not been adequately treated by conventional therapies, the agent is tested in randomized Phase II/III trials at doses already in use. Toxicity is evaluated in advanced-phase studies and the determination of mechanisms of action, the isolation of active components, and the standardization of purity and consistency of agents is desirable, but not necessary, for the development of these agents.

Research that involves botanical products must deal with variation in the concentrations of 'active' ingredients because of genetic and environmental factors (soil, climate, contamination by pesticides, pathogens and other plant species), and extraction procedures. This issue is well-documented in a recent study of the analytical accuracy and reliability of commonly used nutritional supplements in prostate diseases[83]. Measures of the active ingredients of single-agent supplements such as vitamin E, vitamin D, selenium, lycopene and saw-palmetto were determined. Most products showed substantial variability in measured doses with inconsistencies both between and within brands. In particular, saw-palmetto products varied tremendously, with three brands containing virtually no active ingredients. Such inconsistencies might be expected to be magnified when several ingredients are combined in a single product.

The adulteration of natural products with synthetic additives complicates their analysis tremendously, and the problem with PC-SPES is certainly not unique, as the addition of synthetic drugs to herbal products has precedent[84]. In a study by Huang *et al.* of 2609 samples of Chinese herbal medicines collected in Taiwan, 24% contained one or more synthetic compounds including a broad array of nonsteroidal anti-inflammatory drugs, diuretics, corticosteroids, as well as caffeine and sildenafil (Viagra)[85]. In a separate study, Ko reported that 7% of Asian patent medicines collected in California contained undeclared pharmaceutical agents, including ephedrine, methyltestosterone and phenacetin[86]. Despite these liabilities, complex herbal mixtures or the individual botanical agents might still be worthy of further investigation and it is important to remember that several of the most active chemotherapeutic drugs now used in clinical practice are derived from plants.

The second issue is how to study the efficacy of CAM for the treatment of specific diseases. Traditionally, the design and implementation of studies evaluating complementary therapies has been substantially different from the phased approaches that are used to identify and study new chemopreventive or chemotherapeutic agents (BOX 3). Most CAM studies originate from anecdotal reports of efficacy in humans at doses used by the public and that are generally recognized as safe. As a result, Phase I testing to evaluate escalating dose-related toxicities is not performed. Randomized studies are carried out with patient numbers that are anticipated to allow for statistically valid conclusions, but the standardization of compound constituents and activities is not essential for trial design. The pharmacokinetics, tolerability of a range of doses of the agents and the mechanisms by which the agents achieve chemopreventive or antineoplastic effect is secondary, and is pursued after efficacy has been established[2].

A third issue arises regarding the relative advantages of the traditional approach of sequential Phase I–III studies with purified compounds from herbal preparations versus the use of complex mixtures. One disadvantage of assessing individual constituents of complex mixtures is the low likelihood that any single candidate compound will be effective, and the serial testing of numerous compounds over long timelines in adequately powered studies is not tenable. The evaluation of purified compounds that are presumed to be the principal active component of a mixture has its pitfalls. Although the use of complex mixtures certainly doesn't guarantee efficacy, in the event of a negative study, the possibility that the active ingredient was not provided to patients is minimized. However, as the trials involving PC-SPES highlight, the inability to provide quality controls and to standardize mixtures carries an important risk of inappropriate adulteration of products. A marked variation in component concentrations might make it impossible to definitively evaluate efficacy and toxicity. So, it might be necessary to continue the evaluation of complex botanical compounds according to a modified CAM approach. In trials of CAM in Europe, specific constituents of herbal mixtures that are considered to be active components are assayed by liquid chromatography methods and used to keep one or two components of the mixture constant, thereby maintaining some level of quality control and standardization from lot to lot.

In contrast to disease prevention, the argument for initiating randomized studies of CAM using complex mixtures in the setting of active malignant disease without performing traditional Phase I/II studies is less compelling. Follow-up in Phase I and Phase II trials is markedly shorter than in chemoprevention studies, with an attendant decrease in associated costs. Fewer patients need to be treated in Phase II studies to assess the potential for efficacy. Rational evaluation of agents or compounds that are used to treat patients with malignancies requires that pharmacokinetic analysis be performed to assess whether a given dose and frequency achieves detectable levels of agent in serum. In the absence of a defined component, these assays cannot be performed. In addition, for most agents, there is a direct concentration dependence for antineoplastic effect. For this reason, providing the maximally tolerated dose in Phase II testing will minimize the difficulties in deciding whether adequate 'drug' is being provided. Such an approach for the evaluation of CAM therapies might result in the identification of complex mixtures that contain active useful components. The approach classically defined by the National Cancer Institute Drug Development Program (BOX 3) could then be used to identify pure active compounds and a traditional Phase I/II approach to testing of agents could be considered for treatment of patients with a diagnosis of malignancy. The study of CAM in the treatment of chronic disease or prevention could be substantially improved by instituting requirements for standardization and testing of complex herbal preparations similar to those instituted in the United Kingdom and Europe. In many cases, these preparations are being marketed and used to treat specific diseases, which, even under the relatively generous guidelines of the DSHEA, would require more stringent regulatory oversight.

Conclusion

So far, there are no complementary therapies that have been proven through rigorous clinical analysis to reduce the incidence or delay the progression of prostate carcinoma; however, there are many compounds that seem to offer potential benefit, but await validation. One impediment to the completion of these studies involves the widespread uncontrolled access to many of these natural products and their advocated use by support groups, internet chat rooms and the lay press. It is crucial to communicate that vitamin supplements and botanical products are not without risk, either through direct cancer-promoting effects or by interfering with other medical therapies. Although the ATBC study evaluating β-carotene and vitamin E for cancer reduction in male smokers resulted in a 32% decrease in prostate cancer for those men taking vitamin E, there was a 23% increased incidence of prostate cancer for those taking β-carotene — a completely unanticipated result[29]. *Hypericum perforatum* (St. John's wort), *Ginko biloba* (ginko), *Panax ginseng* (ginseng), *Allium sativum* (garlic) and *Piper methysticum* (kava) are widely used herbal remedies that have been shown to affect the metabolism of synthetic drugs and have also been associated with adverse side effects[87,88]. PC-SPES was shown to attenuate the inhibitory effects of taxane chemotherapy on prostate tumour growth in laboratory animals[89].

Until definitive evidence of chemopreventive or antineoplastic effects of supplements or botanical extracts is available, the safest, most affordable and beneficial approach is to consume these substances in their natural state — in complex foodstuffs. An alternative would be to individually assess each patient for deficiencies in specific compounds, such as selenium, and then use supplements to achieve normal physiological levels. It is important that we continue efforts to identify agents from complex mixtures with promising activity, as these have the potential to be used for primary or adjunctive therapy in the prevention and treatment of advanced disease. However, the design of studies to achieve these efforts requires substantial modification to fully evaluate the potential benefits and side effects of each treatment and to prevent the problems that plagued the investigations of PC-SPES.

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