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Complementary and alternative medicine (CAM) in prostate and bladder cancer

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To provide an overview of the scientific and clinical studies underlying the most common vitamin and herbal preparations used in prostate and bladder cancer and evaluate the evidence behind them. A literature search was undertaken on PubMed using various keywords relating to the use of complementary and alternative medicine (CAM) in prostate and bladder cancer. Vitamin E and selenium supplementation can potentially have adverse effects by increasing the risk of prostate cancer. Initial clinical studies of pomegranate and green tea, investigating their chemotherapeutic properties in prostate and bladder cancer have yielded encouraging results. Curcumin, resveratrol, and silibinin have potential anticancer properties through multiple molecular targets; their clinical effectiveness in prostate and bladder cancer is yet to be evaluated. Zyflamend, like PC-SPES, is a combined CAM therapy used in prostate cancer. Acupuncture is popular among patients experiencing hot flushes who are receiving androgen-deprivation therapy for prostate cancer. Conclusive evidence for the use of CAM in prostate and bladder cancer is lacking and not without risk.

Keywords

prostate cancer, bladder cancer, complementary and alternative medicine, vitamin E, selenium, pomegranate, green tea, curcumin, resveratrol, silibinin

Introduction

Complementary and alternative medicine (CAM) is defined by the National Centre for Complementary and Alternative Medicine as a group of diverse medical and healthcare systems, practices and products that are not normally considered to be conventional medicine. There is an increasing popularity and advocacy for the use of CAM amongst patients with cancer, especially prostate cancer. About one in four patients with prostate cancer use at least one CAM method [1]. Prostate cancer shows several attributes that provide attractive intervention points for the application of CAMs. The disease incidence is on the rise with an ageing population; the long latency from intraepithelial malignancy to established prostate cancer provides opportunities for intervention with therapies that are perhaps designed to delay disease initiation or progression [2].

Multiple reasons explain the use of CAM. The trend towards the increased use of CAM is patient-driven and reflects the change in values perceived by patients toward conventional medical treatment. Furthermore, the need for personal control, the perceived safety of a 'natural' product and a search for potential curative therapies when conventional treatments are expected to offer little benefit has driven the surge in the popularity of CAM. Interestingly, non-disclosure of CAM in patients with cancer is 20–77% with common reasons being doctor's lack of enquiry, patient's anticipation of doctor's disapproval and patient's perception that CAM use is irrelevant to their conventional care [3].

Despite its widespread use, little is known about the safety, efficacy, cost effectiveness, and mechanism of action of CAM. The paucity of good quality clinical research does not help patients or practitioners make informed decisions about the efficacy of different types of CAM interventions. In this review, several complementary therapies that can be used in the treatment of urological malignancies, with particular emphasis on prostate and bladder cancer, are discussed. These CAM therapies were selected for review due to their being supported by some scientific evidence derived either from cell-based models, animal models or clinical trials.

Methods

An English language literature search was performed on PubMed to identify key studies investigating the potential chemotherapeutic role of different CAM agents in prostate and bladder cancers. The emphasis was primarily on micronutrients and botanical products that have been the focus of extensive laboratory and epidemiological research directed towards understanding their chemotherapeutic mechanisms in prostate and bladder cancer. Furthermore, we concentrate primarily on clinical data that relates to treatment rather than prevention of prostate and bladder cancer. The search terms included: 'prostate cancer', 'bladder cancer', 'complementary and alternative medicine', 'selenium', 'vitamin E', 'pomegranate', 'green tea', 'curcumin', 'resveratrol', 'silibinin', 'PC-SPES', 'Zyflamend'. The data reviewed included

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experiments involving prostate cancer cell lines, prostate cancer animal models and human clinical trials. Studies on lifestyle or diet change as well as studies on the use of CAM for benign urological disease are not included as this is beyond the scope of this review. However, acupuncture deserved a brief mention due to its apparent widespread use in alleviating side-effects from hormonal treatment in advanced prostate cancer.

Results

Selenium and Vitamin E

Selenium is a non-metallic trace element recognised as a nutrient essential to human health and vitamin E is a family of naturally occurring, essential fat soluble vitamin compounds. There are several potential mechanisms that have been proposed to explain the anti-tumorigenic and antioxidant properties of these compounds. The concept that antioxidants can prevent or treat established malignancy has been reported for many years. This concept is based on the idea that free radicals can attack DNA causing damage, which may ultimately result in tumorigenesis. Other potential mechanisms derived from *in vitro* studies include inhibition of angiogenesis, cellular proliferation and induction of apoptosis [4]. Ample evidence exists from preclinical studies, epidemiological observations, and clinical trials that selenium and vitamin E may prevent the development or progression of prostate cancer and until quite recently both of these compounds were used extensively by patients, both for the prevention and treatment of prostate cancer. In 2009, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) a large-scale, population-based, randomised controlled trial (RCT) reported the results of these agents on the incidence of prostate cancer in North American men [5]. SELECT was designed to assess the effect of selenium and vitamin E, alone and in combination as supplements to a normal diet, on prevention of prostate cancer. In all, 35 533 healthy individuals were randomised in to one of four treatment groups; vitamin E and selenium in combination, selenium and vitamin E alone or placebo. The risk of prostate cancer at a median follow-up of 7 years was increased by 17% in men randomised to supplementation with vitamin E alone, a difference that started to appear ≈3 years after randomisation (hazard ratio 1.17). In addition, the results showed no benefit of selenium alone or when combined with vitamin E for prevention of prostate cancer [6]. Recently, the results of another large multicentre phase III RCT using selenium vs placebo in men with high-grade prostate intraepithelial neoplasia (HGPIN) showed no benefit in the intervention group receiving selenium supplementation [7]. The results of the above studies now challenge the previous notion of a protective role of selenium and vitamin E supplementation with some studies even suggesting the converse.

Initial reports on the effect of selenium levels on bladder cancer incidence have indicated a protective effect of higher selenium levels against bladder cancer suggesting a possible role of selenium as a chemopreventive agent. Three case-control studies reported an increased risk of bladder cancer in people with lower serum selenium concentrations [8]. A meta-analysis of bladder cancer incidence in five observational studies found an inverse association, with an overall risk estimate of 0.67 (95% CI 0.46–0.97), suggesting a protective effect of higher selenium levels against bladder cancer [9]. We found no studies that have assessed the role of selenium as a potential therapeutic agent in patients with bladder cancer. The SELEnium and BLAdder cancer Trial (SELEBLAT) is a phase III randomised multicentre trial, where patients in the intervention arm received 200 μg/day selenium-yeast supplementation during 3 years, with a subsequent follow-up of 3 years, aimed at the prevention of recurrence of non-muscle-invasive bladder cancer. The trial, which is being carried out in Belgium, includes 500 patients with non-muscle-invasive bladder cancer with results expected in 2014 [10].

Pomegranate Extract

The pomegranate (*Punica granatum* L.) fruit has been used for centuries for its medicinal purposes. The active ingredients of pomegranate juice are polyphenol punicalagins and ellagic acid, which have robust antioxidant properties [11]. In addition, pomegranate juice extract can inhibit the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway in prostate cancer cell line experiments, an inflammatory pathway implicated in the pathogenesis of prostate cancer [12]. The first clinical study of pomegranate extract in patients with prostate cancer was conducted by Pantuck et al. [13]; this was a phase II clinical trial that included men with rising PSA levels after treatment with surgery or radiotherapy. Eligible patients had a detectable PSA level of >0.2 and <5 ng/mL and Gleason score of ≤7. Patients were treated with 227 mL of pomegranate juice daily. Clinical endpoints included safety and effect on serum PSA level. The mean PSA doubling time significantly increased with treatment from 15 months at baseline to 54 months after treatment ($P < 0.001$). In addition, the clinical data was accompanied by *in vitro* experiments, where treatment of prostate cancer cell lines with pomegranate extract showed a decrease of 12% in cell proliferation and a 17% increase in apoptosis ($P = 0.005$ and $P < 0.001$, respectively). The statistically significant prolongation in PSA doubling time, coupled with corresponding laboratory effects on prostate cancer cell proliferation and apoptosis *in vitro,* support the rationale that the effects pomegranate juice on PSA kinetics should be investigated in randomised, double-blind, placebo-controlled trials. The interest in pomegranate extract as a potential therapeutic measure in patients with prostate

cancer is reflected by the multiple cancer trials registered with ClinicalTrials.gov database investigating the impact of pomegranate supplementation (NCT01100866, NCT00719030, NCT00336934, NCT00413530, and NCT01220817).

Green Tea

Green tea derived from the plant *Camellia sinensis* has been consumed in the Far East for many centuries. Green tea contains polyphenolic compounds, the most abundant of which is epigallocatechin-3-gallate (EGCG) an antioxidant that is more potent than both vitamin C and E [14]. Suggested mechanisms of the anti-tumorigenic action of green tea include apoptosis and cell cycle arrest via alterations in mitogen-activated protein kinase, phosphatidylinositol-3-kinase (PI3K)/Akt and protein kinase C pathways, inhibition of inflammatory pathways NF-κB and cyclooxygenase-2 (COX-2), and modulation of the IGF and androgen receptor (AR) axes [15]. Specifically EGCG acts as a direct antagonist of androgen action and physically interacts with the ligand binding domain of the AR [16]. Preclinical data on the use of green tea for chemoprevention of prostate cancer were generated using the transgenic adenocarcinoma mouse protocol (TRAMP) model, an animal model of mice that are genetically engineered to develop prostate adenocarcinoma. In this study green tea extract (GTE) was administered orally to TRAMP mice for 24 weeks achieving a 40% reduction in localised prostate tumour development at 20 and 30 weeks. Furthermore, administration of GTE negated the metastatic spread to lymph nodes, liver, lungs and bone improving survival by 70% compared with the control mice [17].

A few clinical trials have been undertaken to assess its therapeutic or chemopreventive properties. A double-blind, placebo-controlled study investigated the effect of consumption of 600 mg GTE/day on progression to prostate cancer in 60 men who were diagnosed with HGPIN. HGPIN is the main pre-malignant lesion of prostate cancer and will result in a substantial number of cancers in a 1-year period [18]. After 1 year of treatment, only one man was diagnosed with prostate cancer among the 30 men that received GTE daily. Whereas, nine cancers were found among the 30 men treated with placebo. The results suggest a 90% chemoprevention efficacy of GTE in men with a high risk of developing prostate cancer ($P < 0.01$) [19]. Serum PSA levels showed a non-significant decrease in GTE-treated men at 9 and 12 months. Overall, the results of this study suggest that administration of GTE could be an effective therapy for premalignant lesions of high-risk men, allowing us to intervene before prostate cancer develops. A 2-year follow-up assessment of the above study was published in 2008 [20]. Despite a significant loss of patient follow-up with only nine participants from the placebo arm and 13 from the GTE arm remaining, the cohort underwent a third biopsy. Two further cancer diagnoses appeared in the placebo arm and one in the GTE arm. Overall, even after suspension of the GTE treatment, the GTE arm had an almost 80% reduction in prostate cancer diagnosis compared with the placebo group [21].

Some studies have also investigated the role of green tea in patients with confirmed prostate cancer. One of the studies was an open-label, single-arm, two-stage phase II clinical trial that evaluated the effects of four capsules of polyphenon E daily containing a total daily dose of 800 mg EGCG administered during the interval between prostate biopsy and radical prostatectomy [22]. Serum was collected before initiation of the drug study and on the day of prostatectomy and analysed with ELISA for levels of different biomarkers. There was a significant decrease in serum PSA, hepatic growth factor (HGF), vascular endothelial growth factor (VEGF), IGF-1 and the ratio of IGF-1 to IGF binding protein 3 (IGFBP-3). The aforementioned biomarkers are used for ascertaining the metastatic and malignant potential of prostate cancer. However, the results of this study must be interpreted with caution as other trials assessing the effects of green tea on prostate cancer biomarkers and progression have not been as successful. A study from Jatoi et al. [23] used a dosing schedule of 6 g green tea/day in water in six divided doses. Only 1 of 42 patients showed a >50% reduction in PSA level and most patients complained of tea toxicity. In conclusion, although green tea appears to have some benefit in the prevention of the progression of HGPIN to prostate cancer, there is no data currently supporting the benefit of increased consumption of green tea amongst men with confirmed prostate cancer.

Evidence supporting the role of green tea in bladder cancer is only restricted to animal models and cell-based studies. A study by Sagara et al. [24] investigated the effect of green tea polyphenol on bladder tumour size and angiogenesis in mice given N-butyl-(-4-hydroxybutyl) nitrosamine (BBN), with and without green tea polyphenol. The results showed that green tea polyphenol had no anti-carcinogenic effect, with all mice exposed to BBN developing bladder cancer; however, green tea polyphenol inhibited tumour growth and invasion in mice with established bladder cancer, mostly through the regulation of angiogenesis. Another cell-based study investigated the growth inhibition and cell cycle arrest effects of EGCG, on the NBT-II bladder tumour cell line. The results suggest that by down-regulating the cyclin D1, cyclin-dependent kinase 4/6 and retinoblastoma protein machinery, EGCG can inhibit growth and promote cell cycle arrest in NBT-II bladder tumour cell lines [25].

Contrary to the initial belief that vitamin E can, through its antioxidant properties, prevent or even treat prostate cancer and at least not cause harm, the SELECT trial strongly refuted this theory, reiterating the importance of being cautious in the

use of botanical products or micronutrients, until definitive evidence of the chemotherapeutic properties of such agents becomes available. Despite this initial setback, further RCTs have yielded promising results with the use of pomegranate extract and green tea. The study by Pantuck et al. [13], which evaluated pomegranate extract in prostate cancer was one of the first studies to show clinical benefit from a CAM in prostate cancer. The results from ongoing RCTs investigating the chemotherapeutic potential of pomegranate and green tea in prostate and bladder cancer will hopefully shed more light on the clinical effectiveness and safety of these CAM methods.

Curcumin

Curcumin is derived from turmeric, the spice that makes curry powder yellow. The interest in its antineoplastic properties stems from epidemiological studies correlating prostate cancer incidence and dietary curcumin intake [26]. The major component of curcumin is the lipophilic polyphenol curcumin I [27]. The anti-cancer activity of curcumin relates to its anti-inflammatory and antiproliferative properties. Curcumin has been shown to suppress the proliferation of both the androgen-dependent prostate cancer cell line LNCaP and the androgen-independent DU145 line [28]. Its mechanism of antiproliferative action is through its influence on multiple signaling pathways. Curcumin can also inhibit VEGF and angiogenesis *in vivo* [29]. Inflammatory mediators, e.g. COX2 and NF-κB, are also down-regulated by curcumin, expression of which has been associated with a higher prostate tumour grade angiogenesis metastatic potential of prostate cancer [30]. The ability of curcumin to potentiate the cytotoxicity of chemotherapy agents in prostate cancer cell line experiments has recently been documented. Specifically, synergism between curcumin and 5-fluorouracil and paclitaxel has been reported [31]. Although, it is apparent from such experiments that curcumin can exert anticancer properties via multiple targets, little is known about the dose required to achieve the same results *in vivo*. Furthermore, clinical trials are needed to fully realise its potential.

Resveratrol

Resveratrol is a polyphenol compound found in the skin of red grapes and other plants. Its potential as a chemopreventive and chemotherapeutic agent has been shown in numerous *in vitro* and *in vivo* studies of human cancers, and like curcumin it can modulate various target and signaling pathways involved in tumorigenesis. The growth inhibitory effects of resveratrol in prostate cancer lie mainly in its effect on the AR, which plays a pivotal role in prostate tumorigenesis. Firstly, resveratrol can regulate AR target gene expression by repressing AR transcriptional activity [32], as well as promoting AR degradation [33]. In addition, resveratrol can repress different classes of androgen-responsive genes, including PSA, human glandular kallikrein-2, AR-specific co-activator and ARA70 in hormone-responsive cells [34], all involved in prostate tumorigenesis and even the development of hormone-refractory prostate cancer [35]. Furthermore, recent studies suggest that it can modulate PI3Ks, which are a family of enzymes involved in cellular functions, e.g. cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. The cellular effects of resveratrol-mediated PI3K inhibition may be partly mediated by inhibition of Forkhead box, class O (FOXO) family tumour suppressor phosphorylation, thereby allowing upregulation of proapoptotic and antiproliferative FOXO targets, e.g. Bcl-2 interacting mediator of cell death (Bim), TNF-related apoptosis inducing ligand (TRAIL), TRAIL death receptors DR5 and DR4, and p27 [36]. Interestingly, resveratrol has anticancer activity in prostate cancer, which can be attributed to modulation of microRNAs. MicroRNAs are small non-coding RNAs that negatively regulate gene expression and have recently received much attention as a cancer therapeutic target. Only a few studies have been published on the effect of resveratrol on bladder cancer cells. These studies, which are mainly cell-based experiments using bladder cancer cell lines, have yielded promising results. In a study by Stocco et al. [37], cells of the bladder cancer cell line ECV304 were incubated with different resveratrol concentrations. Resveratrol induced cell death at high concentrations (>20 μM), but not at low ones (0.1–20 μM). Pretreatment with 2.5 μM protected the cells from oxidative damage, whereas 50 μM intensified cell death and significantly increased the Bad/Bcl-2 ratio, in this way driving the cells to apoptosis in the presence of a high concentration of the pro-apoptotic protein Bad. Another study by Bai et al. [38] using the T24 bladder cell line confirmed that incubation of bladder cancer cells with resveratrol can induce apoptosis through the Bcl-2 family of pro-apoptotic proteins. The use of resveratrol in human trials has proved difficult due to poor oral bioavailability, which is estimated to be 1% with peak plasma concentrations much below the doses used in cell line experiments [39].

Other grape skin extracts, e.g. muscadine grape (*Vitis rotundifolia*) skin extract, which does not contain resveratrol, have also been investigated in prostate cancer. Cell-based experiments have shown that it can induce apoptosis in multiple prostate cancer cell lines by inhibiting Akt signaling [40]. These promising results have led to the initiation of a phase I/II study of muscadine for men with biochemical recurrence of prostate cancer (NCT01317199).

Silibinin

Silibinin is a natural phenol of the flavonolignan family derived from seeds of the milk thistle plant. Evidence exists from animal models of prostate cancer that silibinin can be effective in all stages of tumour progression, not only decreasing the incidence of the tumour itself, but decreasing

metastatic potential and reducing the size of established prostate tumours in the TRAMP murine model. Experiments by Singh et al. [41] in the TRAMP model show that silibinin treatment decreased proliferation and increased apoptosis in TRAMP tumours. A critical underlying factor involved in the steps towards tumour progression is invasion and angiogenesis. Raina et al. [42] showed that silibinin can decrease both VEGF and VEGF receptor 2 levels contributing in this way to the antiangiogenic properties of this agent. In addition, silibinin reduced levels of matrix metalloproteinases-2 and 3 in the TRAMP models, both proteins involved in tumour invasion and metastases. The chemopreventive and chemotherapeutic effects of silibinin in bladder cancer have also been investigated. Intravesical chemotherapy is often used to reduce the risk of recurrence of superficial bladder tumours after transurethral resection. A recent experiment assessed the effectiveness of intravesical silibinin in preventing the recurrence of superficial bladder tumours in rats. This study yielded positive results, suggesting that silibinin can be an effective and novel intravesical agent for bladder cancer [43]. Although silibinin has shown interesting preventative and anticancer properties in prostate and bladder cancer animal models, no human RCTs are underway to investigate the chemotherapeutic effects of silibinin on prostate and bladder cancer.

Despite the lack of evidence from RCTs advocating the use of curcumin, resveratrol and silibinin, cell-based and animal studies have allowed characterisation of the antineoplastic mechanisms of these agents in urological malignancies. The interest in these CAM agents that stems from these pre-clinical studies has led to the initiation of RCTs, which will further evaluate the clinical effectiveness of CAM agents.

Combined CAM Therapy

Several CAM agents exist in combination within the same preparation. The most well-known combined CAM therapy that has been used in prostate cancer is PC-SPES. PC-SPES (BotanicLab, Brea, CA, USA) was a herbal mixture introduced in 1996 consisting of chrysanthemum, isatis, liquorice, *Ganoderma lucidum*, *Panax pseudoginseng*, *Rabdosia rubescens*, saw palmetto, and *scutellaria* (skullcap) [44]. Despite initial convincing laboratory and animal studies indicating potent anticancer properties of PC-SPES that led to the initiation of multiple RCTs, PC-SPES was withdrawn from the market in 2002 due to contamination with prescription drugs, e.g. warfarin. Furthermore, there was a high variation in the composition of the blend between lots. In addition to the contaminants found in PC-SPES, patients reported various adverse effects including gynaecomastia (almost universal), loss of libido, erectile dysfunction, leg cramps, nausea and thromboembolism (≈5% of patients) [45].

A more recent herbal combined therapy familiar to many patients with prostate cancer is Zyflamend (New Chapter Inc., Brattleboro, VT, USA), a herbal blend consisting of extracts from rosemary, turmeric, ginger, holy basil, green tea, hu zhang, Chinese goldthread, barberry, oregano and Chinese skullcap. An *in vitro* study on human prostate cancer cell lines showed inhibition of COX-1 and COX-2 enzymatic activities, cell growth suppression and induced apoptosis [46]. Furthermore, in a mouse model that mimics advanced disease stages, Zyflamend was found to inhibit androgen-dependent and castrate-resistant tumour growth [47]. Robust evidence on the potential role of Zyflamend as a therapeutic agent comes from a phase I clinical trial assessing the effect of Zyflamend with various dietary supplements in 23 men with HGPIN. The results showed that 48% of the men had a 25–50% reduction in PSA levels after 18 months. Nine of 15 patients biopsied at 18 months were found to have benign disease and only two had progressed to carcinoma of the prostate. No serious adverse effects were reported with this preparation [48].

Acupuncture

This CAM method has widespread use, especially in patients undergoing androgen-deprivation therapy (ADT) for prostate cancer. One of the main side-effects of ADT is hot flushes, which have an adverse effect on quality of life [49]. A recent study published by Beer et al. [50] investigated the effect of acupuncture with electrostimulation on 'hot-flush score' (a measure of hot flush frequency and intensity), in a cohort of 22 men receiving ADT; hot-flush related quality of life and sleep quality were also assessed. In all, 41% of patients reported a reduction in hot-flush score of >50%, which was associated with an improvement in the quality of life and sleep after the first 4 weeks of biweekly sessions of acupuncture. The mechanism of action of acupuncture associated with the reduction in hot flushes remains unknown and requires further study. In addition, Beer points out that his study was not randomised and that placebo effect has been shown in previous studies of acupuncture to account for ≈25% improvement in symptoms; the paper states that acupuncture could prove to be a useful non-pharmacological treatment of hot flushes in this cohort of patients.

Conclusions

CAM use is common among patients with prostate and bladder cancer. Pre-clinical data on the mechanism of action of several CAM agents is good, with some of these yielding positive results in human RCTs. However, the undertaking of RCTs to effectively determine the chemotherapeutic potential of such agents in urological malignancies is hampered by the difficulty in achieving meaningful biological concentration in patients. Phase I and pharmacokinetic data from standardised preparations will be needed to determine an appropriate dose and schedule for testing before designing phase II–III trials [28]. To date, there are no CAM therapies that have been

proven through rigorous clinical analysis to reduce the incidence or delay the progression of prostate carcinoma; many agents seem to offer potential benefit, but await validation. Health professionals managing patients with such malignancies should be familiar with CAM and the evidence behind them due to their widespread use. Despite the lack of conclusive evidence advocating the use of CAM in urological malignancies, it will prove difficult for health professionals to refute the use of CAM due to its growing and widespread popularity. The recent scare with the discovery of the association of vitamin E and increased incidence of prostate cancer, in addition to the contaminants isolated from PC-SPES formulation, highlights the need for health professionals to communicate clearly to patients that the use of CAM agents, vitamin supplements and botanical products are not without risk, either through direct cancer promoting effects or by interfering with other medical therapies.

Conflict of Interest

None declared.

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Abbreviations: ADT, androgen-deprivation therapy; AR, androgen receptor; BBN, butyl-(-4-hydroxybutyl) nitrosamine; CAM, complementary and alternative medicine; COX, cyclooxygenase; EGCG, epigallocatechin-3-gallate; GTE, green tea extract; HGPIN, high-grade prostate intraepithelial neoplasia; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PI3K, phosphatidylinositol-3-kinase; RCT, randomised controlled trial; the SELECT, Selenium and Vitamin E Cancer Prevention Trial; TRAMP, transgenic adenocarcinoma mouse protocol (model); VEGF, vascular endothelial growth factor.