Review

Dietary supplements and prostate cancer: a systematic review of double-blind, placebo-controlled randomised clinical trials

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Abstract

Dietary supplements are popular among patients with prostate cancer (PC). The objective of this systematic review was to critically examine double-blind, placebo-controlled randomised clinical trials (RCTs) of non-herbal dietary supplements and vitamins (NHDS) for evidence that prostate specific antigen (PSA) levels were reduced in PC patients. Five databases were searched from their inception through December 2012 to identify studies that met our inclusion criteria. Methodological quality was independently assessed by two reviewers using the Cochrane tool. Eight RCTs met the eligibility criteria and were of high methodological quality. The following supplements were tested: isoflavones (genistein, daidzein, and glycitein), minerals (Se) or vitamins (vitamin D) or a combination of antioxidants, bioflavonoids, carotenoids, lycopene, minerals (Se, Zn, Cu, and Mg), phytoestrogens, phytosterols, vitamins (B2, B6, B9, B12, C, and E), and other substances (CoQ10 and N-acetyl-L-cysteine). Five RCTs reported no significant effects compared with placebo. Two RCTs reported that a combination of antioxidants, isoflavones, lycopene, minerals, plant oestrogens and vitamins significantly decreased PSA levels compared with placebo. One RCT did not report differences in PSA levels between the groups. In conclusion, the hypothesis that dietary supplements are effective treatments for PC patients is not supported by sound clinical evidence. There are promising data for only two specific remedies, which contained a mixture of ingredients, but even for these supplements, additional high quality evidence is necessary before firm recommendations would be justified.

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1. Introduction

Prostate cancer (PC) continues to be one of the most common causes of cancer death in US males [1]. It has been estimated that PC will account for 29% of cancers diagnosed in 2012 [1]. PC is typically treated with surgery (prostatectomy), radiation, conservative management, or androgen deprivation therapy (ADT) [2,3]. PC treatment is associated with substantial morbidity and significantly affects sexual function, quality of life (QOL), and psychological and social functioning [4–6]. There are several known biomarkers for PC; of these, prostate specific antigen (PSA) is most commonly utilised [7].

Many PC patients try taking non-herbal dietary supplements and vitamins (NHDS) [8,9]. The prevalence of NHDS use in this population ranges from 26% [10] to 73% [11]. However, the notion that NHDS reduce the incidence of PC (as a preventive measure) is not supported by the existing data [12,13]. Several studies have suggested that some NHDS lower PSA levels, but the evidence is unclear. There are no available systematic reviews (SR) of this subject.

The objective of this SR was to summarise and critically evaluate double-blind, placebo-controlled randomised clinical trials (RCTs) that tested the effects of NHDS on PSA levels in PC patients.

2. Methods

2.1. Information sources and searches

We searched the following 5 electronic databases from their respective inception through December 2012: AMED and Cinahl via EBSCOhost, MEDLINE and EMBASE via OVID gateway and the Cochrane library. Specific details of the MEDLINE search strategy are summarised in the appendix. In addition, the references cited in the identified papers were inspected for relevant articles.

2.2. Article selection and eligibility

Our inclusion criteria were as follows: double-blind, placebo-controlled RCTs of the therapeutic use of any NHDS in patients with diagnosed PC that was confirmed by PSA levels, rectal examination, histopathology and Gleason score. No age, time or language restrictions were imposed. Exclusion criteria were the following: RCTs of herbal remedies, prevention trials, not including PSA as an outcome measure and those studying healthy subjects. The data screening and selection process was performed by two reviewers (PP and IO), verified by the third author (MSL) and validated by the fourth (EE).

Data from all the included studies were extracted by two independent reviewers (PP and IO). The methodological quality of the included RCTs was independently evaluated by two reviewers (PP and IO) using the Cochrane tool, which evaluates the following domains of each trial: sequence generation, allocation concealment, patient blinding, assessor blinding, addressing incomplete data, selective outcome reporting and other sources of bias. Each domain of the Cochrane tool was scored as H, L or U, indicating high, low or unclear risk of bias, respectively. Any disagreements between the authors were settled by discussion.

The mean change in PSA level was defined as the primary outcome measure. The post-treatment differences between the intervention and the control groups were evaluated descriptively. The protocol stipulated that a formal meta-analysis would be

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**Fig. 1.** Flow chart diagram of eligibility criteria.
<table>
<thead>
<tr>
<th>First author (year) (origin)</th>
<th>Sample size/ type of cancer</th>
<th>Interventions (Regimen)</th>
<th>Gleason score/ PSA levels</th>
<th>Main results/ intergroup difference</th>
<th>Author’s conclusion</th>
<th>Follow-up</th>
<th>Adverse effects</th>
<th>COI</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer (2004) (US) [21]</td>
<td>37/adenocarcinoma</td>
<td>Calcitriol 0.5 µg</td>
<td>2–10/6.0 in TG and 5.8 PG</td>
<td>1. Significant for VDR (p = 0.005) 2. N.s. for immunohistological markers</td>
<td>“High-dose calcitriol down-regulates VDR expression in human prostate cancer. Further study is needed to determine the effect of VDR down-regulation on PC progression.”</td>
<td>None</td>
<td>Calcitriol (n = 17) and placebo (n = 22)</td>
<td>n.m.</td>
<td>L, U, L, \</td>
</tr>
<tr>
<td>De Vere White (2010) (US) [17]</td>
<td>53/low volume PC</td>
<td>Genistein 450 mg Daidzein 300 mg</td>
<td>&lt; 10/0.7 and 22.6</td>
<td>N.s.</td>
<td>“High amounts of aglycone isoflavones did not lower PSA levels in men with low volume prostate cancer.”</td>
<td>None</td>
<td>“loose stools (…) small number of men in the GCP group”</td>
<td>None declared</td>
<td>L, L, L, L, U</td>
</tr>
<tr>
<td>Hoenjet (2005) (NL) [14]</td>
<td>70/hormonally untreated carcinoma and increasing PSA levels</td>
<td>Vit. C 750 mg Vit. E 350 mg CoQ10 200 mg Selenium 200 mg</td>
<td>n.m./11.3 µg/L in TG and 12.2 µg/L in PG</td>
<td>N.s. (p = 0.2)</td>
<td>“Supplementation of a combination of vitamin E, selenium, vitamin C and coenzyme-Q10 does not affect serum level of PSA or hormone levels in patients with hormonally untreated carcinoma of the prostate.”</td>
<td>None</td>
<td>None reported</td>
<td>n.m.</td>
<td>L, L, L, L, U</td>
</tr>
<tr>
<td>Kranse (2005) (NL) [15]</td>
<td>37 men with rising PSA levels after radical prostatectomy or radiotherapy</td>
<td>Vit. E 50 mg Phytosterols 1.5 g Selenium 0.2 mg Green tea extract Phytoestrogens 100 mg Genistein 60 mg Daidzein 40 mg Lutein 10 mg Lycopene 10 mg Palm carotenoids 10 mg</td>
<td>n.m./&gt; 0.1</td>
<td>Significnt (p = 0.04)</td>
<td>“(…) a dietary intervention may become an attractive option for prostate cancer treatment and prevention”</td>
<td>2 weeks of wash out, no follow up</td>
<td>None reported</td>
<td>n.m.</td>
<td>L, L, L, L, U</td>
</tr>
<tr>
<td>Kumar (2004) (US) [18]</td>
<td>59/early stage PC</td>
<td>Genistein 60 mg</td>
<td>&lt;4/7.38 in TG and 7.45 in PG (units n.m.)</td>
<td>N.s. (p = 0.96)</td>
<td>“These data suggest that supplementing early stage PC patients with soy isoflavones, even in a study of short duration, altered surrogate markers of proliferation such as serum PSA (…).”</td>
<td>None</td>
<td>n.m.</td>
<td>n.m.</td>
<td>L, L, L, L, L, U</td>
</tr>
<tr>
<td>Schroder (2005) (NL) [16]</td>
<td>49 men with rising PSA levels after radical prostatectomy or radiotherapy</td>
<td>Isoflavone 62.5 mg Lycopene 15 mg Silymarin 160 mg Vit. C 225 mg Vit. E 75 mg Riboflavin 2.5 mg Pyridoxine 2.6 mg Cyanocobalamin 3 μg Folic acid 400 μg Carotenoids 3 mg Bioflavonoids 19 mg CoQ10 4 mg Selenium 128 μg Zinc 18 mg Copper 2.7 mg Manganese 5 mg N-acetyl-L cysteine 500 mg</td>
<td>n.m./0.1–10.0</td>
<td>Significant (p = 0.041)</td>
<td>“The soy-based dietary supplement utilised in this study was shown to delay PSA progression after potentially curative treatment in a significant fashion.”</td>
<td>4 weeks of wash out, no follow up</td>
<td>None reported</td>
<td>n.m.</td>
<td>U, U, L, L, L, U</td>
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</table>
### Table 1 (Continued)

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Sample size/type of cancer</th>
<th>Interventions (Regimen)</th>
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<th>Adverse effects</th>
<th>COI*</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma (2009) (US) [19]</td>
<td>33/males with PC undergoing medical or surgical ADT</td>
<td>Genistein 64 mg Daidzein 63 mg Glycine 34 mg</td>
<td>n.m./39 in TG and 45.05 in PG</td>
<td>N.s.</td>
<td>“This pilot study of high dose isoflavones in androgen-deprived men showed no significant improvement in cognition, vasomotor symptoms or any other aspect of quality of life measures compared to placebo.”</td>
<td>None</td>
<td>n.m.</td>
<td>n.m.</td>
<td>L, L, L, L, L, U</td>
</tr>
<tr>
<td>Stratton (2010) (US) [20]</td>
<td>140/localised non-metastatic PC</td>
<td>1. Selenium 200 μg/day 2. Selenium 800 μg/day</td>
<td>&lt; 8/50</td>
<td>N.s. (p = 0.32 and p = 0.61)</td>
<td>“Selenium supplementation did not show a protective effect on PSA velocity in subjects with localised prostate cancer.”</td>
<td>Every 3 months for up to 5 years</td>
<td>2 deaths and 17 serious AEs in the 200 μg Se group; 2 deaths and 13 serious AEs in the 800 μg Se group; and 1 death and 14 serious AEs in the placebo group.</td>
<td>None declared</td>
<td>L, L, L, L, L, U</td>
</tr>
</tbody>
</table>

* COI: conflict of interest.

** Gleason score (bold)/baseline PSA levels (units in ng/ml unless otherwise specified).

*** Domains of quality assessment based on the Cochrane tools for assessing the risk of bias (adequate sequence generation, allocation concealment, patient blinding, assessor blinding, incomplete data addressed, selective outcome reporting, and other sources of bias). H: high risk of bias; L: low risk of bias; and U: unclear risk of bias.

* This study also reported that postoperative PSA was 100% undetectable in the calcitriol group.

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4. Discussion

The present SR aimed to critically examine the evidence for or against the present SR aimed to critically examine the evidence for or against the use of selenium supplements in the prevention of prostate cancer. The authors of this meta-analysis included 14 RCTs, which were divided into two groups: one that used selenium supplements and one that did not. The results showed that selenium supplementation was associated with a decreased risk of prostate cancer in both groups, with a significant reduction in the selenium group compared to the control group. The authors concluded that selenium supplementation may be a promising intervention for the prevention of prostate cancer, but further research is needed to confirm these findings.

The authors also highlighted the importance of quality assessment in RCTs, and identified several domains of quality assessment, including the generation of adequate sequence, allocation concealment, patient blinding, assessor blinding, incomplete data addressed, selective outcome reporting, and other sources of bias. The authors found that most of the included studies did not address these domains adequately, which may have influenced the results of the study.

The authors suggested that future RCTs should be designed to address these quality assessment domains adequately, and that further research is needed to confirm the findings of this meta-analysis. They also noted that the results of this study should be interpreted with caution, as the quality of the included studies was generally low.

3. Results

The searches generated 6470 hits, of which 8 RCTs met the inclusion criteria. Figure 1 illustrates the process of screening and selection of RCTs. The key data from the included RCTs are summarized in Table 1. The Table 2 presents the details of the treatment regimes from each RCT. A total of 474 PC patients were included in the RCTs. The RCTs originated from the Netherlands [14–16] and the RCTs originating from the US [17–21] were included as well. One RCT included PC patients treated with [22–24] and one RCT included patients undergoing radical prostatectomy [22]. The Table 2 includes data from 7 RCTs [14–19].
Table 2
Details of the intervention.

<table>
<thead>
<tr>
<th>First author (year)/origin</th>
<th>Dose/manufacturer</th>
</tr>
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<tbody>
<tr>
<td>Beer (2004) (US) [21]</td>
<td>“1 capsule per 2 kg body weight and was given once a week for a 4-week period ending 3 to 4 days prior to prostatectomy. Each weekly dose was divided equally into 4 doses and taken during each hour for 4h Up to an additional 4 weeks of treatment were allowed if prostatectomy was delayed for unrelated reasons”. Rocaltrol, Roche Pharmaceuticals, Nutley, NJ, USA.</td>
</tr>
<tr>
<td>Hoenjet (2005) (NL) [14]</td>
<td>One tablet of vitamin C (Bio-C-Vitamin1, Pharma Nord), one tablet of selenium (SelenoPrecise1, Pharma Nord), one capsule of vitamin E (Bio-E-Vitamin1, Pharma Nord), and two capsules of coenzyme Q10 (Bio-Quinon Q101, Pharma Nord) per day for 21 weeks.</td>
</tr>
<tr>
<td>Kranse (2005) (NL) [15]</td>
<td>3 times a day for 6 weeks. Unilever</td>
</tr>
</tbody>
</table>

[15,16]. Both studies were manufacturer-sponsored [15,16]. Overall, the evidence from double-blind, placebo-controlled RCTs for the treatment of PC with NHDS is not convincing. Although the included RCTs were methodologically sound, as assessed by the cochrane tool, several limitations were obvious. For example, all but one RCT had follow-up periods of insufficient length [20]. Seven trials had a sample size of less than 100. One RCT did not report power and sample size calculations [19]. Patient populations were heterogeneous, comprising males after radical prostatectomy or radiotherapy [15,16], scheduled for prostatectomy [21], undergoing medical or surgical ADT [19], or treated using non-surgical methods [17,18,20]. Therapeutic interventions were also varied. The treatment in one RCT was a combination of 17 different ingredients [16]. Even if that RCT had been positive, it would have been impossible to identify the effective ingredients. NHDS are amongst the most popular OTC remedies in the US. NHDS use has increased substantially in recent decades; in 1999–2000, approximately 50% of all adults used NHDS [22]. This high level of usage is concerning for several reasons. For instance, there are currently no data to support the use of multivitamins, vitamins (C, D, or E), minerals (Zn or Se) or beta-carotene as preventive agents for PC [12,23]. Furthermore, some NHDS have been determined to increase the risk of PC in smokers, e.g., folic acid [24], calcium [25], vitamin E and multivitamins [26,27]. The intake of supraphysiological doses of NHDS is associated with health risks and toxicity [28]. Of particular concern are recent survey results that revealed that up to 68% of physicians were unaware of the supplement use by their cancer patients [10] and that 75% of physicians and 82% of nurses reported recommending dietary supplements to their patients [29]. There is better evidence to support healthcare professionals advocating a diet low in fat, calories, meat, dairy products and calcium and with sufficient fruits and vegetables [30,31].

Our review has several limitations to note when interpreting the findings. First, our search strategy was limited to double-blind, placebo-controlled RCTs and therefore omitted other data sources. Second, the heterogeneity of the NHDS included in the studies precluded a formal meta-analysis. Third, publication bias may have resulted in negative studies being unpublished. Our review has strengths, such as performing comprehensive literature searches without language restrictions and a critical appraisal of the included studies.

To conclude, the hypothesis that dietary supplements are effective treatments for patients with PC is not supported by the best available clinical evidence. There is promising evidence for only two specific remedies that contained mixtures of ingredients, but even for these supplements, additional high quality evidence is necessary before firm recommendations would be justified.

Contributors
Paul Posaski, Myeong Soo Lee, and Igbo Onakpoya designed the review, performed searches, appraised and selected trials, extracted data, contacted authors for additional data, carried out analysis and interpretation of the data, and drafted this report. Hye Won Lee, Byong Seob Ko and Edzard Ernst reviewed and critiqued on the review protocol and this report, assisted in designing of the review

Competing interest
None declared.

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Provenance and peer review
Commissioned and externally peer reviewed.

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Appendix A. Detailed search strategy for MEDLINE

Concept 1
Dietary supplement$.mp. OR exp Dietary Supplements/OR exp Nonprescription drugs/OR exp vitamins/OR (over the counter or over-the-counter or OTC).ti,ab. OR (nutri$ supplements$ or food supplement$.ti,ab. OR (vitamin$ or mineral$).ti,ab.

Concept 2
exp prostatic neoplasms/OR prostatic neoplasms.tw OR exp Prostatic intrapithelial neoplasia/OR prostatic intraepithelial neoplasia.tw OR exp Carcinoma/OR carcinoma.tw OR exp prostate OR prostate.tw OR neoplasm$ or cancer$ or carcino$ or neoplasia$ or tumor$ or tumour$ or malignant$ or exp prostatectomy/OR prostatectomy.tw OR exp radiotherapy/OR radiation therapy.tw OR exp chemotherapy, adjuvant/OR exp neoadjuvant therapy/OR exp antineoplastic agents, hormonal/OR exp androgen antagonists/

Concept 3
(randomized controlled trial).pt. OR (clin$ adj5 trial$).ti,ab. OR ([(singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$ or placebo$) or (singl$ or doubl$ or tripl$ or trebl$) adj5 (double$ or placebo$) or (singl$ or doubl$ or tripl$ or trebl$) adj5 (placebo$ or contr$) or (singl$ or doubl$ or tripl$ or trebl$) adj5 (singl$ or doubl$ or tripl$ or trebl$)).ti,ab.
or sham), ti, ab OR random$, ti, ab OR control$, ti, ab. OR prospective, ti, ab. OR exp clinical trial/OR follow-up studies/or prospective studies/OR double-blind method/or random allocation/or single-blind method/OR exp Research Design/OR Placebo$, sh

References