Dietary supplements and prostate cancer prevention

GIANCARLO MARRA, MARCO ODERDA AND PAOLO GONTERO

Prevention of prostate cancer through the use of dietary supplements is an attractive proposition for patients and doctors. Many patients already turn to supplements, but doctors are not sure what to say when asked for an opinion on their potential benefits. In this article, the authors take a critical look at the evidence for supplements in prostate cancer and find that, in general, the evidence is wanting.

Prostate cancer represents an ideal target for prevention. It has a high incidence, being the most common non-skin solid neoplasm among men. Secondly, it has a long and slowly evolving natural course, with the majority of tumours being diagnosed at a low-risk stage.1,2

Many natural compounds have been investigated for their ability to slow down or possibly stop the natural course of prostate cancer, the most widely studied being vitamin E, selenium, lycopenes, polyphenols and isoflavones. All these compounds yield multiple in vitro and in vivo anticarcinogenic features, such as antioxidant, induction of apoptosis and inhibition of cellular proliferation and angiogenesis.1 These properties, combined with their low toxicity, make them ideal candidates for prostate cancer chemoprevention.

Several observational studies have shown these compounds to have a protective effect. However, the evidence is not unidirectional, as negative studies have also been published and it is important to bear in mind the major limitations of epidemiological studies.2

None of these agents has been proven to prevent prostate cancer in large, randomised controlled trials (RCTs). On the contrary, some of them have recently been linked to an increased risk of developing cancer.

Meta-analyses have shown no significant protective effect against prostate cancer from lycopenes, abundant in red fruit and vegetables such as tomatoes and carrots.
**VITAMIN E AND SELENIUM**

Vitamin E is an essential lipid-soluble antioxidant that has several functions, including regulation of gene expression, enzymes and neurological functions. Its most active form, α-tocopherol, is abundant in plant oils such as soya, corn and olive oil.

Selenium is a trace element and essential micronutrient for both plants and animals, playing a key role in the functioning of antioxidant enzymes. Common sources of dietary selenium include nuts, cereals, mushrooms, fish and meat.

Two RCTs enrolling patients in the early 1990s, initially suggested the protective activities of these compounds (Box 1). The Nutritional Prevention of Cancer (NPC) Trial aimed to test the hypothesis that selenium could decrease the incidence of non-melanoma skin cancer and enrolled 1312 US participants. The results showed selenium to have a significant protective effect, with a 63% reduction in prostate cancer incidence, although the effect was limited to men with lower baseline PSA and low plasma selenium concentrations.

The Alpha-Tocopherol, Beta-carotene Cancer Prevention (ATBC) trial's primary outcome was to investigate lung cancer prevention by randomising 29133 smokers. Men receiving active treatment had a significant 32% and 41% reduction in prostate cancer risk and prostate cancer mortality, respectively.

Although neither of these trials were designed to investigate prostate cancer, based on their promising results, researchers set up the Selenium and Vitamin E Cancer Prevention Trial (SELECT), the largest chemoprevention trial ever performed, randomising 35533 men in four arms to receive either vitamin E, selenium, both supplements or placebo, respectively. Initial results, published in 2009 at a 5.46 years’ follow-up, did not show any protective effect in the three treatment arms when compared to placebo (p<0.0001), but rather suggested a negative, although not statistically significant, effect for the vitamin E arm (relative risk [RR]=1.13, 99% CI 0.95–1.35; p=0.06).

In line with these findings, other trials with selenium did not show any difference to placebo. However, initial findings from the SELECT trial dramatically changed after longer follow-up and subgroup analysis. At an additional 54,464 person-years of follow-up, vitamin E yielded a 17% increased risk of developing prostate cancer (99% CI 1.004–1.36, p=0.008).

Whilst selenium alone and selenium plus vitamin E had a risk of developing prostate cancer similar to placebo at this point, subsequent case-cohort analysis in the selenium supplement group demonstrated the risk of high-grade prostate cancer among men with higher selenium status increased by 91% (p=0.007).

Finally, a recent phase 1/2 RCT looking at selenium, lycopene and polyphenols versus placebo found an increased, non-statistically significant risk in men taking supplements. This may fit with evidence that antioxidant administration may increase the risk of prostate carcinogenesis in animal models and humans with selected genotypes.

**Evidence suggests supplements with vitamin E and/or selenium should be avoided.**

**LYCOPENE AND POLYPHENOLS**

Lycopene is a carotenoid found in tomatoes and other red-coloured fruits and vegetables, including watermelons, pink grapefruit and carrots. The 2007 report from the World Cancer Research Fund suggested there was enough evidence to claim a protective role for lycopene against prostate cancer (Box 2).

However, at the time of the report meta-analysis of 21 case-control, cohort and nested case-control studies suggested that the protective effect of lycopene, if present, is at best modest, with a 1% risk reduction of developing prostate cancer. A more recent meta-analysis, including prospective studies from 1989 to 2011, did not show any significant protection and could not recommend the use of lycopene supplements in the prevention of prostate cancer. While being widely investigated in observational research, only a few small RCTs have looked at lycopene supplements versus placebo, and these did not show significant results.

Polyphenols are natural, water-soluble compounds and are the main constituents of tea. Content varies, depending on species and growing conditions of the plants. Green tea is rich in polyphenols.
**PROSTATE DISEASE**

**Box 2. Lycopenes and polyphenols**

**LYCOPENES**
- Suggested as protective by the World Cancer Research Fund in 2007. However:
  - of two published meta-analyses, one reported only a 1% risk reduction in prostate cancer, whereas the other reported no benefit. Neither study included RCTs
  - only a small number of RCTs have been carried out, all suffering from severe sample size limitations and yielding non-statistically significant results.

**POLYPHENOLS**
- Suggested as protective by epidemiological studies and lower prostate cancer incidence in Asian populations, where green tea consumption is high. However:
  - of two published meta-analyses in 2014, one reported only modest risk reduction in prostate cancer, whereas the other did not report any benefit. Neither study included RCTs
  - only a small number of RCTs have been carried out; one yielded positive findings, whereas the most recent found no significant association.

**COMBINED**
- A recent RCT combining lycopenes, polyphenols and selenium suggested an increased risk of prostate cancer.

Evidence does not suggest any benefit from lycopene or polyphenol supplements.

Based on the correlation between high tea consumption and lower prostate cancer incidence in Asian populations, several observational studies investigated the protective effect of polyphenols. In 2014, two meta-analyses, both including 21 cohort and case-control studies, were published. One reported a reduced prostate cancer risk for men in the highest range of tea consumption, yielding a protective effect on low-grade prostate cancer (odds ratio [OR]=0.66, 95% CI 0.46–0.93), regardless of green or black tea type. The other reported no evidence of a protective effect (OR=0.86, 95% CI 0.69–1.04). The discrepancy may be explained by differences in the databases searched and study periods, leading to selection bias. Neither can be considered conclusive.

In contrast, in epidemiological studies, a significant 90% prostate cancer risk reduction was found by an Italian RCT. Despite a high dropout rate at a two-year follow-up, results were confirmed as statistically significant. However, the recently published results of an American trial, randomising 97 men with precancerous prostatic lesions to receive polyphenol E (green tea extract) or placebo, revealed no significant difference in prostate cancer incidence.

Although not proven dangerous, lycopene and polyphenol have not been proven useful and their use should not be encouraged.

**ISOFLAVONES**
Isoflavones are plant-derived compounds found in soya foods, and are classified as phytoestrogens due to their modest oestrogenic properties. Genistein, daidzein and other isoflavones have been associated with a protective effect against various cancers, including prostate and breast cancer. In vitro studies have shown they can reduce serum testosterone by inhibition of 5 alpha-reductase, the enzyme that metabolises testosterone to its most active form, dihydrotestosterone. Several cross-sectional and case-control studies have shown that isoflavone intake is associated with a dose-dependent decreased risk for prostate cancer (Box 3). Similarly, high isoflavone plasma concentrations have been associated with lower risk of prostate cancer. However, there is also evidence reporting no effect.

In a 2009 meta-analysis, including 15 epidemiological studies on soya consumption and nine on isoflavones in association with prostate cancer risk, soya intake was associated with a 26% risk reduction of developing prostate cancer. However, isoflavones were not protective against prostate cancer (RR/OR=0.88, 95% CI 0.76–1.02). Separate analyses did show isoflavones to be effective in prostate cancer chemoprevention in the Asian population (RR/OR=0.52, 95% CI 0.34–0.81), whereas there was no benefit in the Western population (RR/OR=0.99, 95% CI 0.85–1.16).

A recent meta-analysis included two RCTs using isoflavones in men at clinical risk of prostate cancer. One selected men with a completely negative prostate biopsy, whereas the other included subjects with a diagnosis of precancorous prostatic lesions. A significant reduction in prostate cancer incidence was found with isoflavone (RR=0.49, 95% CI 0.26–0.95).

Data from epidemiological, case-control and in vitro/vivo studies, confirmed by RCTs, suggest that isoflavones are promising chemopreventive compounds. However, this needs to be confirmed by large and well-designed RCTs.

**CALCIUM AND THE REST**
Calcium is another supplement for which observational data yields controversial reports. Several large case-control and cohort studies have demonstrated increased prostate cancer risk for high intake of calcium foods and/or supplements. However, whilst some studies yielded association of high calcium intake with high-risk and fatal prostate cancer, others suggested...
Box 3. Isoflavones and other supplements

**ISOFLAVONES**
- Suggested as protective by several epidemiological and case-control studies, and by lower prostate cancer incidence in Asian populations, where soya consumption is high:
  - a meta-analysis of epidemiological studies reported a 26% risk reduction in prostate cancer. However, isoflavone benefit was limited to Asian population studies, but did not appear significantly protective in Western countries
  - a meta-analysis of two RCTs found a significant prostate cancer risk reduction in men randomised to receive isoflavone supplements.

Evidence suggests benefit from isoflavones supplements in preventing prostate cancer. Further confirmation is needed.

**OTHERS**

**Calcium**
- Suggested as increasing the risk of prostate cancer by several epidemiological studies. No RCTs using calcium supplements and prostate cancer are available.
- Evidence suggests high calcium intake may be associated with an increased risk of developing prostate cancer.

**Vitamins B, D and C, n-acetyl cysteine, minerals other than selenium and others**
- Little evidence.

**SUMMARY**
Despite initial enthusiasm towards natural compounds in preventing prostate cancer, mainly due to observational studies and small RCTs, no definite evidence has been found to support their benefit. Indeed, recent evidence argues that some of these supplements have a negative effect, notably vitamin E and selenium. High calcium intake has also been associated with an increased risk of prostate cancer, although no RCTs are available to prove this.

Men at risk of developing prostate cancer often confuse the benefits of a healthy and balanced diet with those derived from taking nutritional supplements. Almost 50% of all newly diagnosed prostate cancer patients report the use of supplements, and fewer than half have discussed the issue with their physician. Not only are most supplements of no benefit, in some cases their use may lead to an increased risk of developing cancer. In the light of present evidence, men at high risk of developing prostate cancer seeking to use nutritional supplements should be warned about their use. Isoflavones are an exception, but further confirmation of the promising results seen in their use is needed before they can be recommended to patients with confidence.

**Declaration of interests:** none declared.

**REFERENCES**


