Emerging role of nutrients and bio-active food components in prostate cancer chemoprevention

K. Ackaert, S. Joniau, H. Van Poppel

Prostate cancer is generally slow to progress and is therefore considered an ideal candidate for chemoprevention. This review article aims at evaluating the use of soy isoflavones, selenium, alpha-tocopherol, lycopene and green tea catechins as chemopreventive agents for prostate cancer.

(Belg J Med Oncol 2011;5:139-43)

Introduction

Prostate cancer (PCa) is a multifactorial disease with genetic and environmental factors involved in its etiology. Incidence and mortality rates show strong variations worldwide with the highest rates in North America, Australia, Western and Northern Europe and the lowest rates in Asian countries. However, Asian immigrants to the United States adopting a western dietary pattern show a dramatic increase in PCa incidence. It is therefore suggested that dietary modifications play a role in the initiation and progression of PCa. Because of its heterogeneous nature with many patients displaying nonaggressive disease, PCa is an ideal target for chemoprevention, which is defined as the use of specific agents to prevent, delay, or slow down the carcinogenic process. The simplest way for natural chemoprevention is the use of dietary supplements, since most men prefer taking a tablet to changing their dietary habits.

Promising chemopreventive agents in prostate cancer care

Soy isoflavones

Isoflavone intake in Asia mainly originates from soy foods and approximates 50mg per day, which is about ten times as high as Western intakes. The main soy isoflavones are genist(e)in, daidz(e)in and glycit(e)in. The outcome of a meta-analysis of 14 epidemiological studies (8 on isoflavones) suggests that soy and isoflavone consumption is associated with decreased PCa risk. Soy food consumption was associated with a reduction of nearly 26% in PCa risk in men consuming the highest versus the lowest intake.[1] In addition to this, several other studies analysed the effect of soy intake, isoflavone supplementation and serum isoflavone levels on PCa risk. A case-control study evaluating PCa risk in relation to isoflavone, fatty acid and micronutrient contents of the Japanese diet in 200 patients and 200 age-matched controls found isoflavones to be protective against PCa. The odds ratio (OR) for the highest

Authors: Mr. K. Ackaert MD, Department of Urology, AZ Turnhout, Campus St. Elisabeth, Turnhout, Belgium; mr. S. Joniau MD, Department of Urology, UZ Leuven, Campus Gasthuisberg, Leuven, Belgium; mr. H. Van Poppel MD PhD, Department of Urology UZ Leuven, Campus Gasthuisberg, Leuven, Belgium.

Please send all correspondence to: mr. H. Van Poppel MD PhD, Department of Urology UZ Leuven, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium, E-mail hendrik.vanpoppel@uz.kuleuven.ac.be

Conflict of interest: the authors have nothing to disclose and indicate no potential conflicts of interest.

Key words: alpha-tocopherol, chemoprevention, green tea catechins, lycopene, prostate cancer, selenium, soy isoflavones.

(≥89.9 mg/day) compared to the lowest quartile (<30.5 mg/day) of isoflavone intake was 0.42 (95% CI: 0.24–0.72, $P<0.01$).[2] The impact of isoflavone intake was also investigated in a prospective study in Japanese men. Methodological strengths of this study were the large variation in isoflavone consumption, the use of a validated food questionnaire, and its prospective design reducing the probability of recall bias inherent in case-control studies. During follow-up from 1995–2004, 307 men were newly diagnosed with PCa, of which 74 cases were advanced, 220 cases were organ localised, and 13 cases were of an undetermined stage. Men with the highest intake of isoflavones (genistein ≥32.8 mg/day) had a decreased PCa risk compared to those with the lowest intake (genistein <13.2 mg/day). Isoflavone consumption was associated with a dose-dependent decrease in localised PCa risk, with relative risks (RR) for men aged ≥60 years in the highest quartile of genistein, daidzein, and soy food consumption compared to the lowest of 0.52 (95% CI: 0.30–0.90, $P_{trend}= 0.03$), 0.50 (95% CI: 0.28–0.88, $P_{trend}= 0.04$) and 0.52 (95% CI: 0.29–0.90, $P_{trend}= 0.01$), respectively. In contrast, isoflavone consumption tended to be associated with an increase in advanced PCa risk.[3] Prostatic cancer tissue with higher metastatic potential completely or partially loses estrogen receptor (ERβ) expression. Since soy isoflavones reduce PCa risk through ERβ amongst other mechanisms, ERβ loss might be one explanation for the observed effect.

When plasma concentrations of phytoestrogens were examined in relation to subsequent PCa risk in a case-control study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC), higher plasma concentrations of genistein were associated with a lower risk: RR among men in the highest versus the lowest fifth was 0.71 (95% CI: 0.53–0.96, $P_{trend}= 0.03$).[4] A second case-control study nested in the Japan Public Health Center (JPHC)-based prospective cohort study, investigated the association between isoflavones and subsequent PCa. Twenty newly diagnosed cases of PCa were identified. For each case 2 matched controls were selected from the cohort. The researchers found that high plasma genistein (OR: 0.54, 95% CI: 0.29–1.01, $P_{trend}= 0.03$ for highest versus lowest group) was associated with a dose-dependent decreased risk of localised PCa. The findings suggest that plasma isoflavone levels may be protective against the development of localised PCa. They were not significantly associated with advanced PCa risk.[5]

A prospective study in men with isolated high-grade prostatic intraepithelial neoplasia (HGPIN) reported a decrease in PSA levels and a lowered incidence of progression to PCa in response to a 6-month supplementation with 2 tablets of Prevalon® (Madaus, Köln, Germany) per day. One tablet consisted of 100 μg selenium, 30 mg vitamin E, and 50 mg soy isoflavones (21 mg genistin, 17.6 mg daidzin and 11.4 mg glycitin). HGPIN is considered a precursor of PCa. Thus, chemoprevention is highly desirable in these high-risk patients. Throughout the study period PCa risk was 25.0% in the group with stable or decreasing PSA levels (N=48, 67.6%) and 52.2% in the group with increasing PSA levels (N=23, 32.4%) (P=0.0458).[6] Other case-controlled studies are in line with the idea of a PCa protective effect of soy products.[7,8] After dietary supplementation, prostatic isoflavone concentrations exceeded plasma levels, which potentially explains the positive outcomes of these studies. The highest achievable blood level of isoflavones through food intake is considered to be 1 μM. Prostate tissue is able to accumulate isoflavones to potentially anticarcinogenic levels. In a double-blind, placebo-controlled, randomised trial the administration of 82 mg isoflavones per day (27.2 mg total isoflavones/tablet, expressed as aglycone equivalents with 10.6 mg genistein, 13.3 mg daidzein and 3.2 mg glycitein) in 19 men prior to radical prostatectomy (RP), resulted after 2 weeks in a total isoflavone serum level of 0.7 μM and a corresponding prostate tissue level of 2.3 μM.[9]

Nevertheless, other studies have shown negligible benefits in men receiving soy supplementation.[10-12] Feasible reasons for these inconsistent findings are differences in study design, size, doses and/or isoflavone concentrations achieved in the body.

Selenium and vitamin E

The rationale for the use of selenium as a PCa chemopreventive agent comes from a secondary analysis of the Nutritional Prevention of Cancer (NPC) Trial. This skin cancer prevention study found a significant reduction in overall PCa incidence with daily use of 200 μg selenium (RR: 0.51, 95% CI: 0.29–0.87). Despite the fact that no interaction took place between baseline PSA and treatment, the

protective effect of selenium was restricted to those with lower baseline PSA levels (≤4 ng/ml) (RR: 0.35, 95% CI: 0.13–0.87). Only participants with baseline plasma selenium concentrations in the lowest 2 tertiles (<123.2 ng/ml) had significant reductions in PCa incidence. An unadjusted estimate showed a significant 65% reduction in PCa incidence upon selenium supplementation.[13]

Results from a secondary analysis of the Alpha-Tocopherol, Beta-carotene Cancer Prevention (ATBC) study provided a rationale for the use of alpha-tocopherol as PCa chemopreventive agent.[14] In this ATBC lung cancer prevention trial a 32% reduction in PCa incidence (95% CI: 12–47, P=0.002) was detected in participants in clinical (not latent) PCa receiving 50 mg alpha-tocopherol per day. A 41% reduction in PCa mortality (95% CI: 1%–65%) was observed among men in the alpha-tocopherol group from 1985 - 1993.[15] Moreover, higher serum alpha-tocopherol levels at baseline were associated with improved PCa survival with a hazard ratio (HR) of 0.67 (95% CI: 0.45–1.00). The strongest survival relationship was detected for men receiving alpha-tocopherol and who were in the highest serum alpha-tocopherol quintile at baseline (HR: 0.51, 95% CI: 0.20–0.90) or at 3-year follow-up (HR: 0.26, 95% CI: 0.09–0.71).[16] These positive findings contradict those recently reported by the Physicians' Health Study II (PHS II) in which higher alpha-tocopherol dosages were evaluated for shorter periods.[17]

Based on indirect evidences, selenium (200 μg/day) and vitamin E (400 IU/day) were tested separately and in combination for PCa prevention in a randomised, prospective, double-blind, phase III study, known as the Selenium and Vitamin E Cancer Prevention Trial (SELECT). The study was terminated prematurely (at 7 instead of 12 years) since no statistically significant differences in PCa rates were observed among any of the groups.[18] Reasons why selenium and vitamin E, alone or in combination, failed to prevent PCa in the SELECT trial are possibly related to genetic susceptibility or chemical form (in the case of selenium), and dose (for vitamin E). In SELECT pure L-selenomethionine was used. This chemical form might have lost its chemopreventive potential if methionine was randomly inserted into various proteins. The previous NPC trial with the positive outcome was performed with high-selenium yeast containing only 20% of L-selenomethionine, next to a mixture of selenocysteine, Se-methylselenocysteine, selenoethionine, selenoglutathione, selenodiglutathione and selenite (representing another 20%). Future investigations will need to establish if selenium yeast is a better choice in PCa prevention, while considering the long-term safety of anorganic selenium compounds (e.g. selenite) with potential genotoxicity.[19] The vitamin E dose (400 IU alpha-tocopherol/day) in SELECT might have been too high to be effective, as an 8-fold lower dose of 50 mg/day (roughly equivalent to 50 IU/day) produced the earlier positive findings in the ATBC study.[18] Achieving increased plasma or tissue alpha-tocopherol levels within the physiologic range, such as through a 50 mg/day supplement, may be sufficient to obtain a PCa preventive effect. It would also explain why in the PHS II no effect of high dose vitamin E (400 IU every other day, HR: 0.97, 95% CI: 0.85–1.13) was found on PCa incidence during the 8 years follow-up.[17]

Lycopene

A 2007 expertise of the World Cancer Research Fund yielded sufficient body of evidence for a PCa protective effect of lycopene-containing foods. The claim was substantiated by results of investigations with tomatoes (5 cohort studies and 9 case-control studies), trials judging the impact of dietary lycopene (3 cohort studies and 14 case-control studies) and research on serum or plasma lycopene (6 cohort studies and 2 case-control studies) (www.dietandcancerreport.org). Other studies found no correlation between lycopeen and PCa incidence.[20,21] Again, differences in study design, size, dose and/or concentrations achieved in the body, may be reasons for inconsistencies.

Updated results of the Health Professionals Follow-up Study (HPFS), a prospective cohort study, revealed that high lycopene intake was associated with reduced PCa risk (RR for high versus low quintiles is 0.84, 95% CI: 0.73–0.96, P_{trend}=0.003). Intake of tomato sauce, the primary source of bioavailable lycopene, was associated with an even greater PCa risk reduction: RR for more than 2 servings/week versus less than one serving/month is 0.77 (95% CI: 0.66–0.90, P_{trend}=0.001).[22] A large nested case-control study within the prospective HPFS found a statistically significant inverse association between higher plasma lycopene concentrations and lower PCa risk, restricted to participants of ≥65 years at the time of blood donation (OR: 0.47, 95%

Key messages for clinical practice

1. Encouraging results with chemopreventive agents such as soy isoflavones, lycopene, green tea catechins and alpha-tocopherol (at a physiologic dose of approximately 50 mg/day) justify their use in PCa care in high-risk populations.
2. Chemopreventive agents may be most suitable for high-risk patients such as patients with isolated HGPIN, elevated PSA and negative biopsy.
3. Chemopreventive agents may also be appropriate for high-risk groups such as obese men with insulin resistance, or individuals over 40 years of age with elevated PSA levels, rapid PSA velocity or a family history of PCa.

CI: 0.23–0.98) as well as to those without a family history of PCa (OR: 0.43, 95% CI: 0.26–0.89).[23] A phase II clinical trial in men prior to RP reported a reduction in tumour size and plasma PSA level in response to 3 weeks oral supplementation with 30 mg lycopene per day. Twelve of 15 men (84%) in the lycopene group and 5 of 11 men (45%) in the control group had tumour sizes <4 ml (P=0.22). Plasma PSA decreased by 18% in the intervention group, whereas it increased by 14% in the control group (P=0.25).[24] In a 6 months phase II study PCa patients received 2x15 mg lycopene per day (as a tomato extract), either alone or in combination with 2x40 mg soy isoflavones. Thirty-five out of 37 patients in the lycopene group (95%) and 22 out of 33 patients in the lycopene plus soy isoflavone group (67%) achieved stable disease designated as serum PSA stabilisation.[25] Since chemoprevention is probably most effective in early PCa, the fact that lycopene treatment was studied in patients with HGPIN is worth mentioning. In a randomised, double-blind, placebo-controlled study, 40 patients with HGPIN at transurethral resection of the prostate consumed 4 mg lycopene twice daily during 1 year. PCa reduction at the end of treatment was 66%. The authors considered lycopene to be an effective chemopreventive agent in the treatment of HGPIN, without any toxicity and good tolerability.[26]

In fact, lycopene also looks promising for patients diagnosed with benign prostate hyperplasia (BPH). A placebo-controlled pilot study in 40 patients with histologically proven BPH reported a decrease in PSA levels (P<0.05), inhibited disease progression and improved BPH symptoms (P<0.01) in response to 6 months lycopene supplementation (15 mg/day), whereas no changes were noted in the placebo group.[27]

Green tea catechins

A one-year proof-of-principle trial in 2006 assessed the safety and efficacy of green tea catechins (GTC) in 66 HGPIN volunteers. In a double-blind, placebo-controlled manner patients were randomised to 600 mg GTCs per day (3 200 mg capsules) or placebo. Each capsule contained 5.5% (-)-epigallocatechin (EGC), 12.2% (-)-epicatechin (EC), 51.9% (-)-epigallocatechin-3-gallate (EGCG), 6.1% (-)-epicatechin-3-gallate (ECG), 75.7% total GTCs and <1% caffeine. After 1 year, only 1 of 30 GTC-treated men (almost 3%) was found to have PCa compared to 9 out of 30 placebo-treated men (30%). These data suggest a 90% reduction in PCa initation by GTCs administration in men with HGPIN. Secondary observations were changes in lower urinary tract symptoms (LUTS) as assessed by the International Prostate Symptom Score (IPSS) and Quality of Life scores (QoL). IPSS and QoL scores of GTC-treated men with coexistent BPH improved, reaching statistical significance for IPSS.[28] A 2-year follow-up in a subset of patients showed that GTCs had a long-lasting effect on PCa prevention.[29] An open-label, single-arm, 2-stage phase II clinical trial evaluated the effects of supplementation with a standardised green tea extract providing 1.3 g total GTCs (800 mg EGCG) on serum biomarkers in 26 PCa patients during the short interval between prostate biopsy and RP. The results showed a significant reduction in serum PSA levels amongst others.[30]

Conclusions

Physicians must be aware of the chemopreventive opportunities of soy isoflavones, lycopene, green tea catechins, alpha-tocopherol and selenium in PCa care. However, more research on the safety and efficacy of selenium chemical forms is warranted. Due to some neutral results chemopreventive agents are not appropriate for routine recommendation, but are rather to be reserved for high-risk populations.

References

1. Yan L, Spitznagel EL. Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis. Am J Clin Nutr 2009;89:1155–63.
2. Nagata Y, Sonoda T, Mori M, et al. Dietary isoflavones may protect against prostate cancer in Japanese men. J Nutr 2007;137:1974–9.
3. Kurahashi N, Iwasaki M, Sasazuki S, et al. Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. Cancer Epidemiol Biomarkers Prev 2007;16:538–45.
4. Travis RC, Spencer EA, Allen NE, et al. Plasma phyto-oestrogens and prostate cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2009;100:1817–23.
5. Kurahashi N, Iwasaki M, Inoue M, et al. Plasma isoflavones and subsequent risk of prostate cancer in a nested case-control study: the Japan Public Health Center. J Clin Oncol 2008;26:5923–9.
6. Joniau S, Goeman L, Roskams T, et al. Effect of nutritional supplement challenge in patients with isolated high-grade prostatic intraepithelial neoplasia. Urology 2007;69:1102–6.
7. Jacobsen BK, Knutsen SF, Fraser GE. Does high soymilk intake reduce prostate cancer incidence? The Adventist Health Study (United States). Cancer Causes Control 1998;9:553–7.
8. Heald CL, Ritchie MR, Bolton-Smith C, et al. Phyto-oestrogens and risk of prostate cancer in Scottish men. Br J Nutr 2007;98:388–96.
9. Gardner CD, Oelrich B, Liu JP, et al. Prostatic soy isoflavone concentrations exceed serum levels after dietary supplementation. Prostate 2009;69:719-26.
10. Hussain M, Banerjee M, Sarkar FH, et al. Soy isoflavones in the treatment of prostate cancer. Nutr Cancer 2003;47:111–7.
11. Spentzos D, Mantzoros C, Regan MM, Morrissey et al. Minimal effect of a low-fat/high soy diet for asymptomatic, hormonally naive prostate cancer patients. Clin Cancer Res 2003;9:3282–7.
12. Vaishampayan U, Hussain M, Banerjee M, et al. Lycopene and soy isoflavones in the treatment of prostate cancer. Nutr Cancer 2007;59:1–7.
13. Duffield-Lillico AJ, Dalkin BL, Reid ME, et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int 2003;91:608–12.
14. The Alpha-Tocopherol BCCPSG. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med 1994;330:1029–35.
15. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst 1998;90:440–6.
16. Watters JL, Gail MH, Weinstein SJ, et al. Associations between alpha-tocopherol, beta-carotene, and retinol and prostate cancer survival. Cancer Res 2009;69:3833–41.
17. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomised controlled trial. JAMA 2009;301:52–62.
18. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301:39–51.
19. Goossens ME, Buntinx F, Zeegers MP. Selenium and vitamin E: interesting biology and dashed hope. J Natl Cancer Inst 2009;101:1363-4.
20. Kristal AR, Arnold KB, Neuhouser ML, et al. Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol 2010;172:566–77.
21. Peters U, Leitzmann MF, Chatterjee N, et al. Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev 2007;16:962–8.
22. Giovannucci E, Rimm EB, Liu Y, et al. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 2002;94:391–8.
23. Wu K, Erdman JW Jr, Schwartz SJ, et al. Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2004;13:260–9.
24. Kucuk O, Sarkar FH, Sakr W, et al. Phase II randomised clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomarkers Prev 2001;10:861–8.
25. Vaishampayan U, Hussain M, Banerjee M, et al. Lycopene and soy isoflavones in the treatment of prostate cancer. Nutr Cancer 2007;59:1–7.
26. Mohanty NK, Saxena S, Singh UP, et al. Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. Urol Oncol 2005;23:383–5.
27. Schwarz S, Obermuller-Jevic UC, Hellmis E, et al. Lycopene inhibits disease progression in patients with benign prostate hyperplasia. J Nutr 2008;138:49–53.
28. Bettuzzi S, Brausi M, Rizzi F, et al. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. Cancer Res 2006;66:1234–40.
29. Brausi M, Rizzi F, Bettuzzi S. Chemoprevention of human prostate cancer by green tea catechins: 2 years later. A follow-up update. Eur Urol 2008;54:472–3.
30. McLarty J, Bigelow RL, Smith M, et al. Tea polyphenols decrease serum levels of prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients and inhibit production of hepatocyte growth factor and vascular endothelial growth factor in vitro. Cancer Prev Res 2009;2:673–82.