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Randomized, Double-Blind, Placebo-Controlled Crossover Study in Men with Prostate Cancer and Rising PSA: Effectiveness of a Dietary Supplement

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Abstract

Objectives: Epidemiological studies have shown significant relationships between the use of dietary components and prostate cancer incidence and mortality. Large studies of primary prevention, which confirm these findings, are desirable but costly and difficult to design. The present tertiary prevention study reports on the effect of a dietary supplement in comparison with placebo on the rate of increase of prostate-specific antigen (PSA).

Methods: 49 patients with a history of prostate cancer and rising PSA levels after radical prostatectomy ($n = 34$) or radiotherapy ($n = 15$) participated in a randomised, double-blind, placebo-controlled crossover study of a dietary supplement. Ethical approval of the protocol was obtained. Treatment periods of 10 weeks were separated by a 4-week washout period. The supplement consisted of soy, isoflavones, lycopene, silymarin and antioxidants as main ingredients. Changes in the rate of increase of PSA (PSA slope and doubling time) were the primary parameters of efficacy. Analyses according to intention to treat (ITT) and per protocol (PP) were carried out.

Results: Baseline parameters did not differ between randomised groups. Five participants were lost to follow-up, however 46 could be evaluated in an ITT analysis. PP analysis could be performed in 42 men with at least 5 PSA measurements. Per protocol analysis showed a significant decrease in PSA slope ($p = 0.030$) and ^{2}log PSA slope ($p = 0.041$). This translates into a 2.6 fold increase in the PSA doubling time from 445 to 1150 days for the supplement and placebo periods. No treatment-based changes in safety parameters were observed during the study.

Conclusions: The soy-based dietary supplement utilised in this study was shown to delay PSA progression after potentially curative treatment in a significant fashion. More extensive studies of the supplement may be indicated.

Keywords: Prostate cancer; Prevention; Dietary supplement; PSA slope; PSA doubling time

1. Objectives

Epidemiological evidence strongly supports the possibility that the incidence of clinical prostate cancer depends on lifestyle factors, mainly related to diet. Several groups of compounds have been identified as likely candidates. These include components of soy, anti-oxidants and several vitamins. Recent comprehensive reviews are available [1,2]. Evidence from two prospective randomised studies showed that selenium and Vitamin E reduced the relative risk of prostate

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cancer incidence cq mortality utilised as secondary endpoints in these studies [3,4]. Later re-analyses of these trials partially confirmed the original data. A critical evaluation of the available evidence is presented by Moyad [5]. Nevertheless, the findings have led to the establishment of the "Selenium and Vitamin E chemoprevention trial (SELECT)" of the National Institute of Health of the USA. This trial is in the process of recruiting 32,000 participants from 300 different sites at an estimated cost of 150–175 million USD [5–7]. Performing trials addressing primary prevention as the SELECT trial does, may be the only way to definitely show effectiveness of a given regimen. Different and less costly rapid screening approaches are however needed to evaluate effectiveness and properties of potentially preventive regimens, their appropriate dosages and the added value of combining such substances. This cannot be done in primary prevention studies. An international working group of academic and industry related participants suggested the use of PSA based phase II studies in patients with minimal (recurrent) prostate cancer (PC) in combination with animal models of human prostate cancer as a screening tool for new compounds. The regimen can be applied to hormone naive and hormone unresponsive prostate cancer [8]. There is ample evidence that various substances can decrease serum PSA levels without affecting tumour mass [9]. The recommended algorithm therefore utilises nude mice carrying human prostate cancer, a system, which allows to correlate changes in serum PSA in the mouse to changes in tumour mass over time [8]. The suggested algorithm is shown in Fig. 1. It has been applied to several studies [10–12]. The study presented here reports as a first step on the effect of a self-designed dietary supplement in men with minimal residual prostate cancer in a randomised, double-blind, placebo-controlled study.

The patent pending nutritional supplement contained soy isoflavones, lycopene, silymarin, and a balanced mixture of antioxidants (see Table 1). This supplement was designed to interfere with different processes by multiple components at non-toxic dose. The selected components were shown in the past to interfere with different pathways that are involved in the progression of the disease [13–15]. An unpublished document explaining in detail with 28 references the choice and dosage of the components is part of the protocol. Space does not permit its inclusion.

To our knowledge only one clinical intervention study with a single food extract or extracts has been able to show statistically significant reduction of PSA slopes or levels. Hussain et al. 2003 did show a significant slope reduction with 100 mg of an isofla-

Table 1
Composition of supplement and placebo

Ingredients (per daily dose)	Supplement	Placebo	Unit
Soy isoflavone aglycones (ADM Novasoy)	62.5	–	mg
Lycopene (Lyc-O-Mato)	15	–	mg
Silymarin (Milk thistle)	160	–	mg
Ascorbic acid	225	–	mg
Alpha-tocopherol	75	–	mg
Carotenoids	3	–	mg
Bioflavonoids	19	–	mg
Ubiquinol (Co Q10)	4	–	mg
Selenium	128	–	mcg
Zinc	18	–	mg
Copper	2.7	–	mg
Manganese	5	–	mg
Riboflavin	2.5	–	mg
Pyridoxine	2.6	–	mg
Cyanocobalamin	3	–	mcg
Folic acid	400	–	mcg
N-acetyl-L-cysteine	500	–	mg
Calcium carbonate	1148	1871	mg
Prosolv 90	1440	2332	mg
Croscarmellose sodium	144	234	mg
Crospovidone	64	104	mg
Stearic acid	120	195	mg
Magnesium stearate	16	26	mg
Silicon dioxide	24	39	mg

[a] Number of tablets per day: 4.

	Phase II study Positive (by PSA response) / negative	Experimental confirmation Positive / negative	Action
1	-	-	Discard drug
2	-	+	Kinetics? Dose? Adjustment? Discard drug?
3	+	-	Traditional phase II
4	+	+	Phase III study

Fig. 1. Algorithm, proposal for PSA based phase II and III studies.

vone mixture in 41 patients [13]. Other studies did not reach significance [16–18]. Ansari and Gupta [19] combined lycopene (4 mg/day) with orchidectomy ($n = 27$) and were able to show a more reliable and consistent decrease in serum PSA level when compared to orchidectomy alone ($n = 27$). These data support the idea that different targets and different interventions need to be addressed to obtain statistically significant and clinically relevant inhibition of serum PSA by a food supplement.

2. Methods

2.1. Subjects

Patients with a rising PSA after radical prostatectomy or radiotherapy with curative intent were eligible for this study. Patients qualified if their serum PSA was found to rise to levels between 0.1 and 10.0 ng/mL on at least two occasions within an interval of three months and if they had a life expectancy of at least 12 months.

Excluded were men who had prior hormone therapy of any type including Finasteride, chemotherapy, radiotherapy or a transureteral resection of the prostate, which led to an ongoing decrease of PSA at the time of study entry. Men with insulin dependend diabetes mellitus, food allergies, chronic liver diseases, severe gastro-intestinal dysfunctions, dietary restrictions rendering dietary intervention impossible and current use of soy diet were also excluded. A distance from their home to the Erasmus Medical Centre Rotterdam of more than 75 kilometres was unacceptable for logistic reasons.

All participants were recruited from the institution of the principal investigator (F.H. Schröder) and from one affiliated institution in the neighbourhood. The data were collected by the trial office (screening unit) of the department of Urology.

The original protocol was approved by the institutional review board (IRB) of Erasmus MC Rotterdam on August 30, 2000. The study was conducted in full conformance with the principles of the declaration of Helsinki (52nd WMA general assembly Edinburgh, Scotland, October 2000). Written informed consent was obtained from all participants prior to entry.

2.2. Study design

The present study was performed according to a randomised, placebo-controlled, double-blind crossover design of two periods of ten weeks separated by a wash-out period of 4 weeks. The aim of the study was to assess the effect of a soy-based dietary supplement on the slope of the ^{2}log transformed serum prostate-specific antigen (PSA) concentration, compared to placebo in subjects with a history of prostate cancer and rising serum PSA levels. A secondary aim of the study was to assess the effect of the supplement on the slope of the non-transformed serum PSA concentration as well as on the absolute change in serum PSA levels. Our hypothesis was that the slope of the consecutive PSA measurements would be decreased during supplement treatment period compared to the slope during placebo treatment.

At the randomisation visit subjects were randomised over two supplementation groups (group I and II). Subjects in group I first received placebo for 10 weeks during period A, followed by a wash-out period of 4 weeks and subsequently the potentially active dietary supplement for 10 weeks during period B. Subjects in group II received the supplement during period A and placebo during period B. The participants had to take two times two tablets of the dietary supplement or placebo per day. The tablets were number coded and the code was deposited at the hospital pharmacy for emergency use which never occurred. Table 1 shows the composition of the supplement and of the placebo tablets per daily dosage.

Subjects agreed to adhere to their regular diet for the study period and not to use any other dietary supplements. Subjects attended the hospital every two weeks for blood sampling to determine serum total PSA and free PSA levels. Safety information and information on compliance parameters (plasma genistein, daidzin and equol, study medication count.and dietary diaries) was obtained at regular intervals with blood sampling. At least 90% compliance on the product was collected using questionnaires and laboratory values such as liver and kidney function tests. Adverse events were reported to the study co-ordinator and registered.

The study design is shown in Fig. 2.

2.3. Laboratory analyses

All PSA determinations were carried out centrally in the clinical laboratory of Erasmus MC Rotterdam making use of the Beckman-Coulter Hybritech Access technology. Regular quality control measures have shown that interassay variation is limited to less than 5% [20,21].

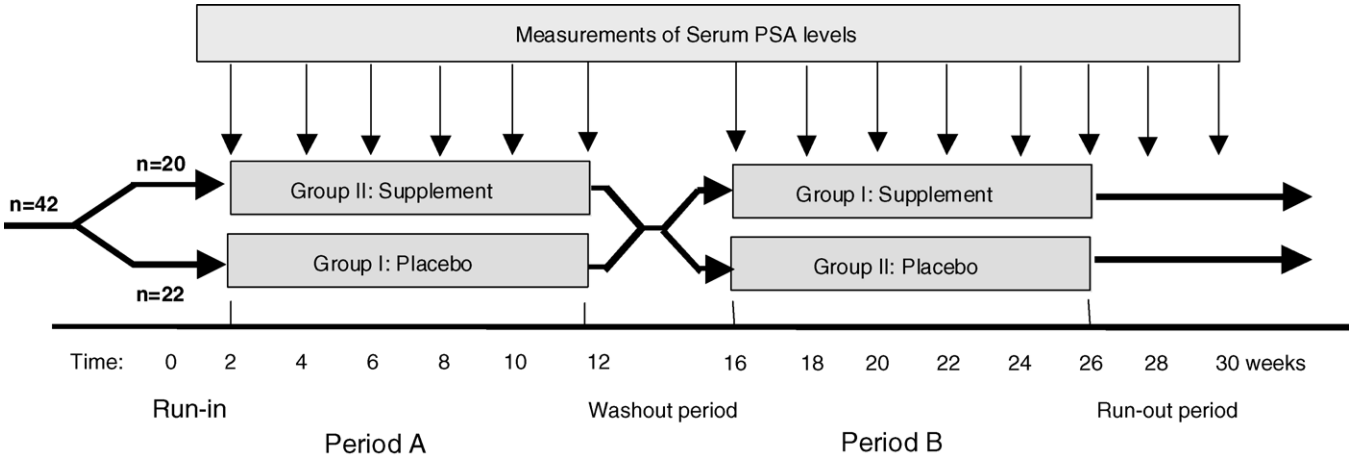

Fig. 2. Study design and time schedule.

Additionally the following parameters were assessed at baseline and at the end of each study period: plasma vascular endothelial growth factor (VEGF) levels, plasma hormone levels (testosterone, dihydrotestosterone, luteinizing hormone and sex-hormone binding globulin), plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), and several nutritional laboratory parameters (plasma Vitamin A, Vitamin E), plasma uric acid, plasma cysteine, plasma cysteinyl glycin, homocystein and plasma isoflavone levels (daidzein, geinistein and equol).

2.4. Statistical analyses

The sample-size calculation in the original protocol were based on a previously performed pilot study and resulted in a required number of subjects of 80 to detect a 83% reduction in PSA slope at an overall significance level of 0.05 and a power of 80%.

Statistical analyses were performed for all randomised subjects with at least two PSA measurements available to allow calculation of PSA slopes, (ITT, intention to treat), and per protocol, PP), excluding non-compliers. Subjects were considered compliant when they fulfilled all in- and exclusion criteria and at least 5 PSA measurements were available for each study period with adequate supplement compliance (>80%). Results are expressed as mean ± standard deviation (SD) and were considered to be statistically significant if the significance levels reached <0.05. Statistical analyses were performed using SPSS 11.0 for windows (SPSS Inc.).

^{2}log and non-transformed PSA slopes were calculated using linear regression for both study periods. PSA doubling times were calculated as the natural log of 2 divided by the slope of the relationship between the log of PSA and time of PSA measurement.

Normality was tested by using the Kolmogorov-Smirnov test. Differences in ^{2}log PSA slopes were tested by Mann Whitney *U* test because of a non-normal distribution. The presence or absence of a carry-over effect from periods A to B was evaluated.

3. Results

Participants were recruited from November 2000 until June 2002. 49 patients with a history of prostate cancer and rising PSA levels after radical prostatectomy ($n = 34$) or radiotherapy ($n = 15$) participated in this randomised double-blind, placebo-controlled crossover study of a dietary supplement.

Five patients were lost to follow up, however 46 patients could be evaluated in an intention to treat analysis. An analysis including patients in whom at least 5 PSA measurements were recorded could be performed in 42 participants. (Fig. 3). Two patients were withdrawn because of <80% compliance.

No statistically significant carryover effect was detected ($p = 0.131$) allowing statistical testing according to the crossover design. Unblinding of the study revealed that 24 were randomised to group I (placebo followed by the supplement) and 25 to group II (supplement followed by placebo). Early termination occurred twice in group I and three times in group II for the following reasons: group I: relapse and lymph nodes and start-in of homone treatment, complaints of palpitations, dizziness and motility problems. Group II: need to undergo vascular surgery, gastro-intestinal complaints (adverse event), carcinoma of the stomach. Three patients had only one PSA determination available for either study period and were excluded from the ITT analyses. Four patients were excluded from the PP analyses: two patients had less than five PSA values available and two patients showed non-compliance for supplement intake.

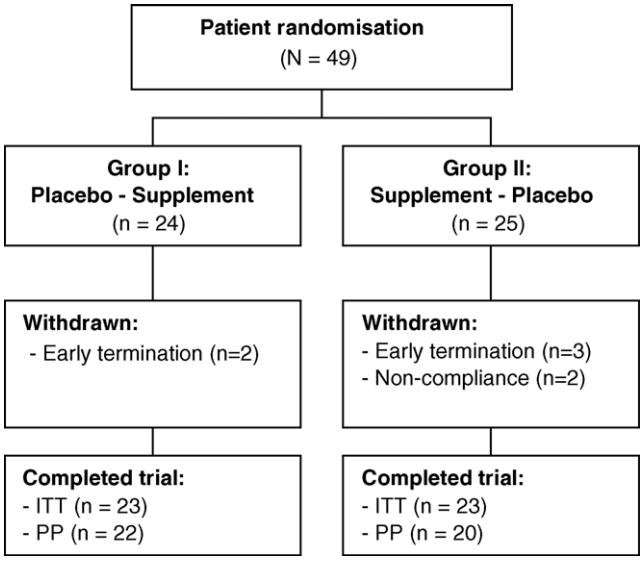

Fig. 3. Flow diagram.

The baseline characteristics of participants and baseline parameters are shown in Table 2 for the whole study population and the two randomisation groups. No statistically significant differences were encountered with respect to physical characteristics, age distribution, distribution of total PSA, stage distribution and treatment modalities.

Results of both the ITT analysis and the PP analysis showed that the slope of the ^{2}log transformed PSA concentrations improved with the supplement in comparison with placebo. Improvement reached statistical significance in the PP population ($p = 0.041$) and showed a trend in the ITT population ($p = 0.089$). Detailed results are shown in Table 3a. The results with respect to ^{2}log total PSA slopes comparing the supplement and control periods are shown in Fig. 4. The median total PSA doubling time for the supplement periods amounts to 1150 days and to 445 days for the placebo periods in the PP population.

Similar results were obtained for the differences in slopes of the non-transformed total PSA concentrations. The absolute changes of total PSA within the two study groups are shown in Table 3b, showing non-significant trends. No differences were found with respect to free PSA. Free PSA values were extremely

Table 2
Characteristics of participants and baseline parameters

Parameter	Complete study $N = 49$	ITT population $N = 46$	PP population $N = 42$
Age (y)	69.8 (±7.1)	69.7 (±7.1)	69.8 (±7.0)
Body weight (kg)	82.0 (±9.2)	82.0 (±9.4)	82.3 (±9.5)
Body mass index (kg/m^2)	26.4 (±2.4)	26.4 (±2.5)	26.6 (±2.5)
Baseline PSA (ng/mL)	3.29 (±4.13) $n = 47$	1.5 (0.2–36.0)	1.5 (0.2–22.0)
Years since diagnosis			
<1	1 (2%)	1 (2%)	1 (2%)
1–3	11 (22%)	11 (24%)	10 (24%)
3–6	24 (49%)	21 (46%)	18 (43%)
6–10	8 (16%)	8 (17%)	8 (19%)
>10	3 (6%)	3 (7%)	3 (7%)
Information not available	2 (4%)	2 (4%)	2 (5%)

low and often non-measurable. Meaningful differences in slopes could not be detected in any of the settings.

Statistically significant changes between supplement and placebo were seen for homocystein, which was reduced by about 30% with supplement medication and cholesterol which was significantly lower by about 4% during placebo (Table 4). Besides, significant increases of Vitamin E, daidzein and genestein levels were seen with the use of the supplement. Compliance was subject to continuous evaluation (see methods). Compliance was >90% in 41 of the 46 participants.

3.1. Carryover effect

Although no statistically significant carryover effects were detected for PSA study parameters, a tendency for a carryover effect was observed for the slope of ^{2}log total PSA in the PP population ($p = 0.131$). When this potential carryover effect was studied more in detail, it was mainly present in the group receiving the supplement followed by placebo (group II) and not in the group receiving placebo followed by the supplement. Based on this finding, and to avoid any misinterpretation of study data, an additional statistical test was performed according to a parallel study design, including only the unpaired data of the two randomisation groups during period A.

Results of this parallel-group testing showed that even between subjects, statistically significant differences in ^{2}log PSA slope were detected between the supplement and placebo ($p = 0.038$). The p-Values for slopes of absolute total PSA and absolute change of total PSA were 0.087 and 0.215 in this parallel-group analysis.

3.2. Safety evaluation

No significant differences were seen between supplement groups or any of the safety parameters listed in the method section. The study team judged the few adverse events seen as not related to the study or the use of the dietary supplement.

These statements apply for baseline characteristics and change over time in both study periods. Hormone levels (testosterone, dihydrotestorene, sex hormone binding globulin, luteinizing hormone) did not change over time and no differences were seen between placebo and supplement periods.

4. Discussion

Complementary and alternative medicine is increasingly used in men with manifest prostate cancer but

Table 3a
Effects of Supplement and Placebo on the slope of the serum total PSA concentration. Slopes are shown for the ^{2}log transformed as well as the absolute data (ug/L.d)[a,b]

Study population	Between-subjects		Within-subjects	p-Value
	Supplement	Placebo	Δ Supplement-Placebo	
Slope of the ^{2}log serum total PSA concentration (ug/L.d)	0.0009 (−0.008–0.014)	0.0022 (−0.004–0.014)	−0.0011 (−0.020–0.010)	0.041*
Slope of non-transformed serum total PSA concentration (ug/L.d)	0.0010 (−0.041–0.279)	0.0025 (−0.003–0.110)	−0.0015 (0.080–0.170)	0.030*

[a] Values are Median (range).
[b] p-Value based on Mann Whitney-U test on within-subject differences between Supplement and Placebo.
* Statistically significant difference between supplement and placebo.

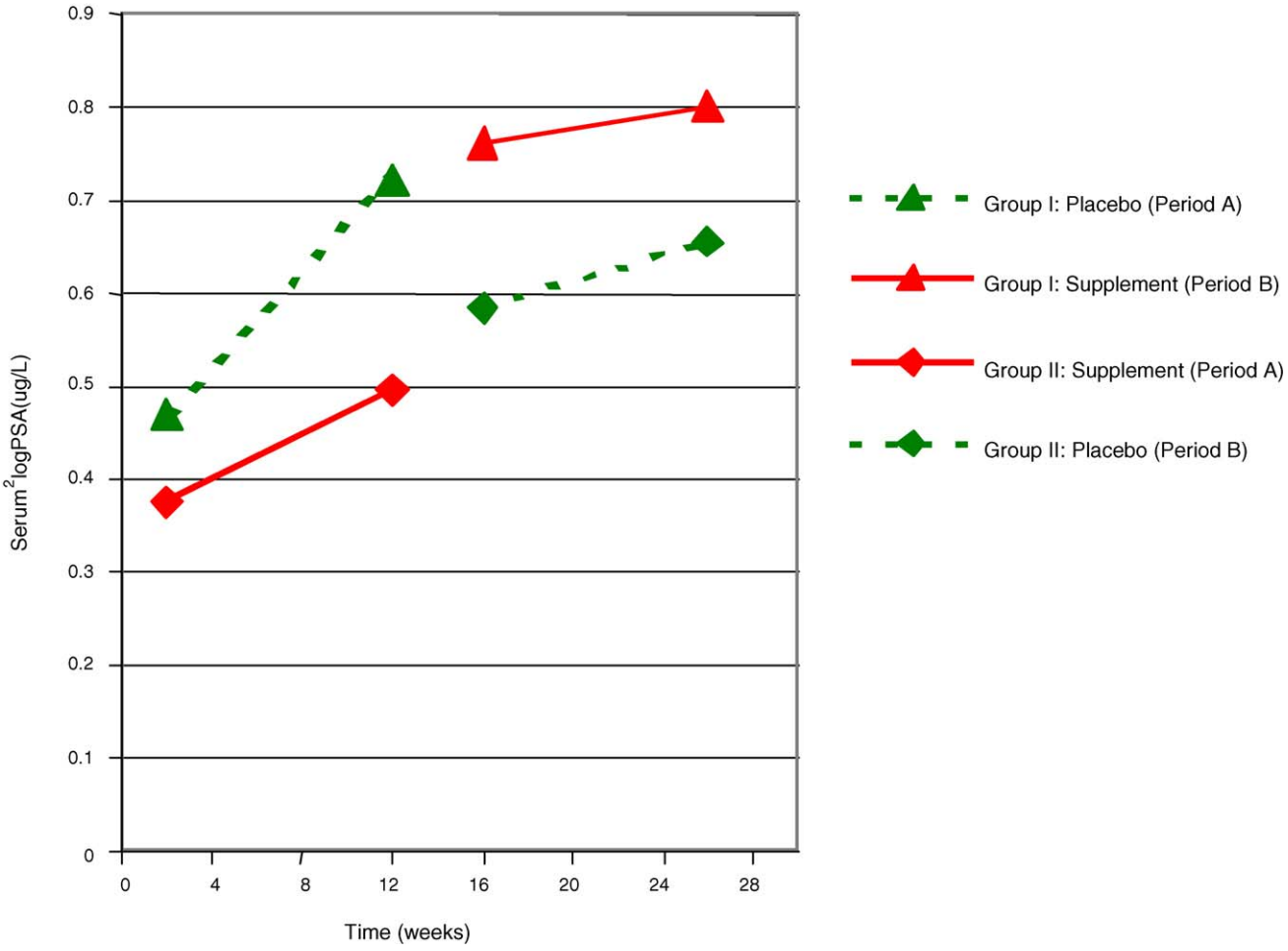

Fig. 4. Slopes of ^{2}log total PSA concentrations during supplement and control periods.

also by men at risk who wish to take preventive measures. Recent surveys showed that 51% of 333 men with risk factors for the development of prostate cancer used dietary supplements while another survey conducted in Canada revealed 39% of complementary and alternative medicine used in men who were diagnosed recently with prostate cancer [22,23]. While there is strong epidemiological evidence that environmental factors including diet are determinants of prostate cancer incidence there is no definite proof so far of preventive properties of any of these agents. Space does not permit to review the available epidemiological and animal experimental evidence, which is for a large part supportive of the results of the present study. Recent reviews however are available [1,2,24].

The present study utilises a self-designed dietary supplement which contains most of the substances that have been shown by epidemiological studies, case-control or phase I and II studies as well as animal experimentation to have a potential to be effective in the prevention of prostate cancer. This randomised, placebo-controlled, double-blind crossover study in

Table 3b
Absolute changes in serum total and free PSA concentrations during administration of Supplement and Placebo ($n = 42$)[a,b]

	Supplement		Placebo		p-Value
	Baseline	Change	Baseline	Change	
Serum total PSA concentration (ug/L)	1.50 (0.2–22.0)	0.10 (−2.00–17.00)	1.50 (0.2–15.0)	0.10 (−0.10–8.00)	0.076
Serum free PSA concentration (ug/L)	0.10 (0.00–2.90)	0.00 (−0.10–4.50)	0.10 (0.10–6.50)	0.00 (0.00–1.40)	0.988

[a] Values are Median (range).
[b] p-Value based on Mann Whitney-U test on within-subject differences between PSAControl and Placebo.

Table 4
Changes in blood lipids, vitamins and other laboratory parameters during supplement and placebo use[a,b]

	Supplement ($n = 42$)		Placebo ($n = 42$)		p-Value
	Baseline	Change	Baseline	Change	
- Total cholesterol (mmol/L)	5.55 ± 0.15	0.005 ± 0.061	5.60 ± 0.15	−0.221 ± 0.067	0.023*
- HDL-cholesterol (mmol/L)	1.42 ± 0.07	0.014 ± 0.026	1.45 ± 0.07	−0.006 ± 0.032	0.650
- LDL-cholesterol (mmol/L)	3.52 ± 0.13	−0.036 ± 0.087	3.50 ± 0.15	−0.128 ± 0.060	0.444
- Cholesterol/HDL ratio	4.28 ± 0.24	−0.130 ± 0.087	4.25 ± 0.25	−0.174 ± 0.079	0.630
- Triglycerides (mmol/L)	1.71 ± 0.21	0.104 ± 0.070	1.85 ± 0.23	−0.092 ± 0.092	0.115
- Vascular epithelial growth factor (VEGF; pg/mL)[b]	48 (24–25000)	5 (−163–3085)	47 (28–14052)	5 (−215–14818)	0.767
- Immunoglobulin F (ng/mL)	12650 ± 1142	−267 ± 920	12672 ± 1274	−705 ± 826	0.535
- Homocystein (umol/L)	13.3 ± 0.6	−4.0 ± 0.4	12.4 ± 0.6	0.2 ± 0.3	<0.001
Vitamin A (umol/L)	2.3 ± 0.1	0.1 ± 0.1	2.3 ± 0.1	0.2 ± 0.1	0.399
Vitamin E (umol/L)	31.0 ± 2.1	8.2 ± 2.1	29.3 ± 1.8	0.2 ± 1.9	<0.001
Uric acid (umol/L)	301 ± 9	1 ± 5	305 ± 10	1 ± 6	0.805
Cystein (umol/L)	185.1 ± 4.8	9.0 ± 4.6	187.5 ± 4.4	3.4 ± 5.0	0.473
Cysteinyl glycin (umol/L)	31.8 ± 0.9	−1.9 ± 0.8	31.7 ± 1.1	−1.5 ± 1.2	0.731
Daidzein (ug/L)	0.0 ± 0.0	273.2 ± 28.7	0.5 ± 0.5	0.0 ± 0.0	<0.001
Genistein (ug/L)	0.0 ± 0.0	490.9 ± 35.5	1.1 ± 1.1	0.2 ± 0.2	<0.001

[a] Values are Mean ± SEM, or Median (Range).
[b] Statistical test on within-subject differences between Supplement and Placebo by Analysis of Variance in case of Normal distribution; else by Mann-Whitney-*U* test.
* Significant, $p < 0.05$.

patients with minimal recurrent prostate cancer (tertiary prevention) shows effectiveness of this supplement by significantly reducing the slope of total PSA during periods of utilisation of the supplement with respect to the placebo periods. The slopes found translate into median total PSA doubling times of 1150 days for the supplement and 445 days for the placebo periods. Obviously, this prolongation of PSA doubling time by a factor of 2.6 would be of great clinical relevance if it would translate into a similar delay in tumour growth. Studies in PSA producing human xenografts in orthotopic transplantation into nude mice are being conducted to confirm the effect on serum PSA and to relate this effect to changes in the speed of growth of the transplanted human prostate cancer tissue. According to the algorithm developed by this group [8] a positive PSA based clinical study and a positive animal study showing an effect on PSA increase and tumour mass would lead to a recommendation of a phase III study in this case meaning a randomised prevention study with utilisation of different endpoints. Men with rising PSA may however consider the use of a dietary supplement anyway to delay the rise of PSA because PSA change is often experienced as a worrisome symptom.

4.1. Other studies (proof of concept)

Several other studies have been conducted within the last 5 years to validate the concept of speeding up the development of new drugs or of preventive agents by PSA based phase II studies in patients with minimal disease, hormone dependent or hormone independent and to confirm that an effect on PSA slope/doubling time also relates to an effect on tumour growth by the use of the animal models developed and available in the departmental laboratory [25]. Another study of a dietary supplement was conducted and yielded confirmatory results with a less pronounced effect on PSA doubling time [10]. This supplement was not applied to the animal system for funding reasons. Another study utilising lycopene and Vitamin E has been concluded in the animal setting using the human prostate cancer line PC346 in orthotopic transplantation. This study shows a significant effect on the rate of increase of PSA and on tumour mass in the animal system. The effect is most pronounced with a combination of both agents [26]. The human randomised study using lycopene and Vitamin E in a placebo-controlled, double-blind crossover fashion is still ongoing.

4.2. Other evidence

Isoflavones from soy including the well-studied daidzein and genistein are major components of what has been termed ‘‘eastern diet’’ with supposed preventive properties for at least prostate and breast cancer [27]. More recent reviews and original experimental reports are confirmatory [28–32].

Evidence relating to tomato products and to lycopene, the red colour of the tomato, has recently been reviewed in [33]. Lycopene as well as selenium and Vitamin E have antioxidant function. Recent evidence has been summarised also for selenium [5,34,35].

Higher selenium levels in plasma and in toenails have been shown to be inversely related to prostate cancer risk [36,37]. The original findings of the Finnish α-tocopherol, β-carotene cancer prevention (ATBC) study, which show a significant reduction of prostate cancer incidence and mortality as a secondary endpoint [4] are not confirmed with long-term follow-up of the same population of periods of 6–8 years [38].

5. Conclusions

Results of this study showed that the dietary supplement significantly improved the slope of ^{2}log transformed PSA concentrations in comparison with placebo. ($p = 0.041$) The differences in ^{2}log transformed total PSA slopes between the supplement and placebo translate into a 2.6 fold increase in PSA doubling time with the use of the supplement. No effects on free PSA concentrations could be detected. The supplement did not effect plasma testosterone, dihydrotestosterone, SHGB or luteinising hormone levels.

The use of the supplement appears to be safe. No adverse events occurred that can be related to the study supplement. No detrimental changes of the safety laboratory parameters were detected. The results of this study must be confirmed preferably in a phase III setting of longer duration.

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Editorial Comment

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Prostate cancer has been shown to be a prime target for chemoprevention. Several studies and observations have linked the diet with its genesis and progression. Dietary interventions have therefore been investigated both in animal models, but also as recently in prospective randomised trials.

Anti-oxidants like Vitamin E, selenium and lycopene have been shown to dramatically inhibit prostate cancer development in animal models [1]. Prospective trials are underway using e.g. Vitamin E or selenium as a preventive mean against the occurrence of prostate cancer. Chemoprevention can be either primary, thus preventing the occurrence of clinically significant prostate cancer, decreasing the incidence in patients with no cancer or poor lesions to cancer slowing down the pace in patients with pre-neoplastic lesions and evident risk factors.

Cancer prevention can also be secondary, thus reducing the recurrence of the disease in patients with a local disease that was treated with a primary treatment, most of the time locally. Rising PSA after local curative treatment for prostate cancer, whether radical prostatectomy or radiation therapy, is an extremely common scenario and optimal therapy is more than controversial. This scenario clearly represents a possibility of secondary prevention by dietary compounds or chemoprevention. It is also an ideal scenario because the vital risks are reduced for this patients population, since a minority and not a majority of patients experiencing this PSA relapse will actually die from the disease, this is true at least on 8–10 years follow-up data.

It is also an exciting field where plenty of clinical studies using biological modifiers, chemotherapeutical regimens and others are currently investigated. In the present study, the results of this randomised double-blind placebo controlled study in men with prostate cancer and rising PSA show that soy-based dietary supplements used were able to delay PSA progression in a significant fashion. The data observed in the therapeutic area demonstrated a 2 to 4 fold increase in PSA doubling time for the supplement as compared to placebo. These data are certainly interesting and deserve further studies. But caution should be given to these observations as well.

First of all, the number of patients included in the trial is extremely limited when one considers the reservoir of patients with rising PSA. Whether these findings can be translated into larger populations is possible but not granted. The second observation is that the type of dietary compounds is of utmost importance in the modulation of the PSA response. The authors recently published a paper with a somehow similar randomised double-blind placebo controlled study using a dietary supplement called Verum [2], in the form of a water-dissolvable powder to be taken 3 times a day and 20 g of margarine per day. Components of the dietary supplement are detailed hereunder (see

COMPOSITION OF THE DIETARY SUPPLEMENT (AMOUNTS PER DAY)

Component
Margarine (20 g)
Vitamin E (50 mg - tocopherol)
Phytosterols (1.5 g)1
Selenium (0.2 mg organic selenium in 0.5 g bakers yeast)
Placebo beverage (3 servings of 200 ml/day)
Caffeine similar to supplement
Beverage (3 servings of 200 ml/day)
Green tea2
Isoflavones3
100 mg phytoestrogens
60 mg genestein
40 mg daidzein
Carotinoids
10 mg luteine
10 mg lycopene
10 mg palm carotenoids (including some - carotinoids)

Table 1) and should be compared to the ones presented by the authors in Table 1 in the main article.

The amount of Vitamin E - lycopene is slightly different and obviously many more dietary supplements are components of the supplements used in the present study. In their study using Verum, results were slightly less convincing, although total PSA slope and free PSA slope were affected as well. The exact reasons why the current supplement was more effective than the Verum on PSA doubling time are unresolved, although the composition of the dietary supplement most likely is of utmost importance in the explanation. Moreover, it does not clearly appear why the authors have changed the dietary compound from Verum to the new components and what prompted them to do so?

However, such small series (37 patients in the Verum study and 49 patients in the present study) make it hard to determine whether the patients population was also responsible for differences in outcome. Whether the impact on PSA slope will correlate in a stabilisation or a decrease of the tumor mass also remains unsolved.

It is also interesting to see that in patients taking soy products, soy was unable to drive significant effects on serum total and free PSA, although it was efficient to reduce low-density lipoprotein cholesterol, estimated coronary arteries diseases and serum concentration of oxidised low-density lipoproteins [3].

This kind of randomised double-blind studies is to be encouraged and the authors should be congratulated for having embarked on these studies. Unfortunately, before recommendations can be made to the general public about the possibility to modulate PSA increases and prostate cancer biology by dietary compounds as a secondary chemopreventive measure, we definitely need larger studies and a better standardisation and characterisation of the effects of each compound on prostate cancer biology.. These limitations should not be seen in any way as barriers to further investigate this exciting field.

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