Effect of a Nutritional Supplement Containing Vitamin E, Selenium, Vitamin C and Coenzyme Q10 on Serum PSA in Patients with Hormonally Untreated Carcinoma of the Prostate: A Randomised Placebo-Controlled Study


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Accepted 9 November 2004
Available online 24 December 2004

Abstract

Objective: To assess the effect of a nutritional supplement containing vitamin E, selenium, vitamin C and coenzyme Q10 on changes in serum levels of PSA in patients with hormonally untreated carcinoma of the prostate and rising serum PSA levels.

Methods: Eighty patients were randomised to receive a daily supplement with either vitamin E, selenium, vitamin C, coenzyme Q10 (intervention group) or placebo over 21 weeks. Serum levels of PSA were assessed at baseline (T0), 6, 13, 19, 20 and 21 weeks. Mean changes in log serum level of PSA, testosterone, dihydrotestosterone, luteinizing hormone and sex hormone binding globulin over 21 weeks between the verum and the placebo group were compared by analysis of covariance.

Results: Seventy patients completed the study (36 verum; 34 placebo). Compliance was >90% in all patients. In the intervention group, plasma levels of vitamin E, selenium and coenzyme Q10 increased significantly over the 21 weeks study period. No significant differences in serum levels of PSA, testosterone, dihydrotestosterone, luteinizing hormone or sex hormone binding globulin (p > 0.2) were observed between the intervention and control group.

Conclusion: Our results indicate that 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.

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Keywords: Vitamin E; Vitamin C; Selenium; Coenzyme Q10; Prostate cancer; PSA; Nutrition; Anti-oxidants

1. Introduction

Prostate cancer has become the second most common cancer in men in Europe and the USA. The incidence of clinically malignant disease is highest in black North American men and is 30-fold higher than in Japanese men [1]. For Japanese migrants to the USA, the incidence increases to about half of the indigenous population within one to two generations, suggesting that dietary and environmental factors, rather than genetic factors, are responsible for the high incidence western countries [2].

Numerous dietary factors have been studied as an etiologic factor in the development of prostate cancer, such as soy protein, animal fat, fibres and micro-
nutrients like vitamin E, selenium, vitamin D, carotenoids, vitamin A, lycopene, vitamin C and coenzyme Q10 [3]. A review of prospective cohort and intervention studies on the aetiology of prostate cancer was recently published [4]. The authors concluded that there are many indications that the development and progression of prostate cancer may be influenced by diet and dietary nutrients, although there is no formal proof for this statement. Two chemoprevention studies, one on selenium and one on vitamin E, have shown, as a secondary finding, that these supplements may have a protective effect on prostate cancer occurrence, with a decreased incidence and mortality [5,6]. For vitamin C, a synergistic effect with the antioxidative effects of vitamin E and selenium has been reported [7]. Preliminary studies with coenzyme Q10 suggested potential clinical efficacy in patients with prostate cancer [8,9]. However, all these results need further confirmation in a rigorous randomized design.

So far, very little information exists on the potential impact of diet or specific nutrients in slowing down the progression of prostate cancer in patients with rising serum levels of PSA. The only randomised clinical intervention study performed to date in men with prostate cancer and rising serum levels of PSA, was a placebo-controlled cross-over study initiated by Schröder and Dagnelie [10] testing the effect of a mixed supplement containing soy, extracts from tea, carotenoids, phytosterols, selenium and vitamin E on serum levels of PSA. The authors reported a nonsignificant delay of 8 weeks of the previous rise in PSA during the 6-week administration of the supplement.

The present study was designed to gain more insight in the possible growth inhibitory effects of the above-mentioned supplements on prostate cancer. Based on the literature [4–10] these supplements are promising candidates to influence the natural course of prostate cancer, because of their potentially synergistic growth inhibitory effect.

The rationale for using a mixture instead of single supplements was twofold. First, there is evidence for synergistic effects. In a number of studies, the combination of selenium and vitamin E has shown to be more effective than each agent alone in inhibiting tumor growth [11]. Also, vitamin C, vitamin E and selenium are part of a synergistic and mutually replenishing biochemical system involving other molecules such as glutathione, zinc and beta-carotene [12].

Our second rationale for using a combined supplement was that, in a “proof of concept” study, chances to achieve a positive effect can be increased by combining a number of promising candidate nutrients in one supplement. Individual antioxidants produce varying degrees of tumour regression in vivo, only at very high doses, which frequently cause toxicity, especially with retinoid derivates. At lower doses they may be ineffective when given as a single agent. Thus a mixture of supplements might be more effective in reducing tumor growth than single vitamins.

## 2. Materials and methods

### 2.1. Subjects

Subjects were recruited at the Urology outpatient clinics of Maastricht University Hospital and clinical centres of Heerlen, Roermond and Sittard. A total of eighty patients were included. Inclusion criteria are shown in Table 1. Taking nutritional and herbal supplements at low dosage was not an exclusion criterion, but such supplements were recorded and patients were asked not to take any new supplements during the study. Based on a significance level of 5% and power of 90%, it was calculated that 20 patients in each arm would be needed in order to detect an average difference of 5% in increase in PSA between the intervention and placebo groups. In order to account for additional sources of variability the sample size in each arm was increased by 10 patients and an additional 10 patients to account for potential dropouts, giving a total of 40 patients per treatment arm.

### Table 1

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>• Histological proven prostate cancer.</td>
<td>• Previous or concurrent hormonal treatment, except when</td>
</tr>
<tr>
<td>• PSA &gt; 4 ng/ml and rising, i.e. two consecutive rises of PSA with at least 2-month interval</td>
<td>of limited duration (≤6 months) as (neo-) adjuvant treatment with curative radiotherapy or radical prostatectomy. The hormonal treatment should have been stopped at least 6 months prior to participation in this study</td>
</tr>
<tr>
<td>• Patients on watchful waiting without hormonal therapy, meeting one of the following criteria:</td>
<td>• Bone metastases</td>
</tr>
<tr>
<td>A. cT1-4 Nx M0 (with no curative treatment because of co-morbidity or decreased life-expectancy),</td>
<td>• PSA &gt; 40 ng/ml</td>
</tr>
<tr>
<td>B. cT1-4 N+ M0, C. Rising PSA after radical prostatectomy or curative radiotherapy.</td>
<td>• Alkaline phosphatase &gt; 2× upper limit of normal value</td>
</tr>
<tr>
<td>• WHO performance 0–2.</td>
<td></td>
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<tr>
<td>• Written informed consent.</td>
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</table>
2.2. Study design
The study was designed as a randomised, double blind, placebo-controlled trial. Patients were assigned to the intervention group or the placebo group according to a randomisation schedule prepared at the Department of Epidemiology of Maastricht University after pre-stratification by tumour stage: (A) cT1–4 N0 M0, no curative treatment because of co-morbidity or decreased life-expectancy, (B) cT1–4 N+ M0, regional lymph node metastases and (C) rising PSA after radical prostatectomy or curative radiotherapy.

2.3. Intervention
Patients randomised to the intervention group were asked to take one tablet of vitamin C (750 mg Bio-C-Vitamine®, Pharma Nord), one tablet of selenium (200 μg SelenoPrecise®, Pharma Nord), one capsule of vitamin E (350 mg Bio-E-Vitamine®, Pharma Nord), and two capsules of coenzyme Q10 (2×100 mg Bio-Quinon Q10®, Pharma Nord) per day for 21 weeks.

All supplements were taken before breakfast, with a second tablet of coenzyme Q10 being taken before dinner. No specific dietary recommendations were given, but patients were asked not to change their diet during the study.

Compliance was checked in two ways: first, by counting the number of tablets handed out to the patients and recollected at the end of the study, and secondly by measuring plasma levels of vitamin E and triglycerides at baseline (t = 2 weeks) and at the end of the intervention (t = 21 weeks). In addition, plasma levels of vitamin C, selenium and coenzyme Q10 were measured in participants from the University Hospital of Maastricht.

2.4. Food frequency questionnaire
The patients filled out a self-administered food frequency questionnaire two weeks prior to the start of the study and at the end of the study. The questionnaire covered consumption over the past month of 253 items from 20 food categories, mainly contributors of vitamin C, vitamin E and selenium. An open-ended section at the end of each food group allowed patients to enter any other frequently eaten foods not listed in the questionnaire. In addition, a section with questions on vitamin and mineral supplement use was included. The patients were asked to indicate the frequency of consumption of these items per day, per week or per month. A trained dietician checked all completed questionnaires for accuracy and completeness. Each food item was converted to daily intake in g by applying a standard portion size according to the food items using the Dutch Measures, Weights and Code numbers 1997. [13] Intake of vitamin E, vitamin C and selenium was calculated using the Dutch NEVO Food Composition Table 2001 [14].

2.5. Blood sampling and outcome assessment
Blood samples were taken by one person (K.H.) in a standardised fashion, and collected in standard test tubes containing anticoagulant. The test tubes from all participating hospitals were transported immediately to one central laboratory for analysis. The primary outcome of the study was the change in serum levels of PSA during the 21-week intervention period. Secondary outcome measures were change in serum levels of testosterone, dihydrotestosterone (DHT), luteinizing hormone (LH) and sex hormone binding globulin (SHBG). Serum values of the supplements and hormones were determined once at baseline and once at the end of the study. Serum levels of PSA were assessed three times at baseline (t = 2, t = 0 weeks), during the study at 6 and 13 weeks and three times at the end of the study (19, 20 and 21 weeks).

At every outpatient visit, patients were asked to report any possible adverse effects or unusual symptoms.

2.6. Statistical analysis
Plasma concentrations of vitamin E were expressed relative to triglyceride levels, because plasma vitamin E depends on triglyceride levels [15]. Because of the exponential distribution of serum PSA levels, PSA values were analysed as log PSA. The biological variability of PSA according to the literature is relatively high (10–20%); Nixon et al. found the biological variability (= within subject) of total PSA to be 7.5% on a day-to-day basis [16]. In our study, the within-subject variability as calculated from 3 repeated blood samplings, taken at one-week intervals at baseline (i.e. at week –2, –1, and 0) amounted to 9%. In order to decrease within-subject variability of PSA measurements, the average values of log PSA obtained at t = −2, 1 and 0 weeks (baseline) and at 19, 20 and 21 weeks (post-intervention) were used for analysis. It can be calculated that by doing so, the standard error is reduced from 9% to 9%/√3≈5%.

The analytical variability between different laboratories is approximately 3–8% [16]. In order to eliminate the analytical variability between different clinical centres, all biochemical analyses were performed in one external laboratory.

Statistical analysis was performed as follows: First, we calculated mean and 95% confidence intervals (CI) of vitamin E, vitamin C, selenium, coenzyme Q10, testosterone, DHT, LH and SHBG within the intervention and placebo groups, and compared the pre- and post-intervention levels in each group. The same analyses were performed for PSA, but here we calculated the geometrical mean instead of the mean. Analysis of co-variance was then used to appraise between-group differences in change of serum levels of PSA, supplements and hormones. Two-tailed p-values below 0.05 indicated statistical significance.

3. Results
Fifty patients with rising serum levels of PSA after radical prostatectomy or curative radiotherapy, and thirty patients with no curative treatment because of co-morbidity or decreased life expectancy were included in the study. No patients with regional lymph node metastases were included. There were no differences in baseline parameters between the subgroups. Five patients were excluded for having a serum PSA >40 μg/l at baseline average on week −2, −1 and 0. During the study, one patient died of a mesenterial infarction, not related to this study. Four patients stopped participation during the study because of lack of motivation. As a result, 70 patients were available for analysis. Eighty patients were included in the study; mean age of the included patients was 73.9 years (range 54–85 years).

The PSA doubling time prior to the study was 68 months for the intervention group and 51 months for the placebo group. The difference was not statistically significant. All biochemical analyses during the study were performed in one external laboratory, Euregio
Table 2
Serum concentrations of vitamin E, selenium, vitamin C and coenzyme Q10 in prostate cancer patients before and after intervention

<table>
<thead>
<tr>
<th>Serum concentrations</th>
<th>Group</th>
<th>Number of patients</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coenzyme Q10 (μg/l)</td>
<td>Verum</td>
<td>14</td>
<td>1452 [1133–1771]</td>
<td>2630 [2148–3113]</td>
<td>1178 [573–1783]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values represent means [95% confidence intervals], and p-values refer to the difference in change between the verum and placebo group.

Table 3
Serum PSA levels in prostate cancer patients before and after intervention

<table>
<thead>
<tr>
<th>Serum concentration</th>
<th>Group</th>
<th>Number of patients</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>34</td>
<td>12.2 [9.9–15.1]</td>
<td>13.4 [9.8–18.2]</td>
<td>1.1 [0.9–1.4]</td>
<td></td>
</tr>
</tbody>
</table>

Values represent geometrical means [95% confidence intervals], and p-value refers to difference in change between the verum and placebo group.

Laboratory Services, Valkenburg, The Netherlands. We used the PSA-immuno-assay Elecsys 1010/1020, Roche Switzerland. The charge-to-charge variability during the study period was ±3%. The median intra-assay variability was ±2% and the week-to-week variability ±3%.

Based on collecting the remaining supplements from the patients at the end of the study, compliance was estimated to be >90% in all 70 patients who completed the study. The supplements were well tolerated and no side effects were reported by any of the participants.

Table 3 shows the effects of the intervention on serum PSA levels of PSA are shown. Geometrical means of serum levels of PSA in the intervention group were 11.3 [95%CI: 9.0–14.2] μg/l at baseline and 14.4 [95%CI: 11.5–18.1] μg/l post-intervention, i.e. an increase by 1.3 [1.2–1.4] μg/l. In the placebo group, PSA was 12.2 [95%CI: 9.9–15.1] μg/l before the study and 13.4 [95%CI: 9.8–18.2] μg/l after the study, i.e. an increase by 1.1 [0.9–1.4] μg/l. The difference in PSA change during the study between the intervention and placebo groups was not statistically significant (p = 0.67).

Serum values of vitamin E, selenium, vitamin C and coenzyme Q10 before and after intervention are shown in Table 2. In the intervention group, serum levels of vitamin E increased by 9 [95%CI: 5–13] μmol per mmol triglycerides (p = 0.001), selenium by 60 [29–91] μg/l (p < 0.001), and coenzyme Q10 by 1178 [573–1784] μg/l (p = 0.001) during the study, whereas vitamin C showed a non-significant decrease by –8 [–23–8] μmol/l (p = 0.76). In contrast, in the placebo group none of the plasma levels of these supplements changed significantly during the study. The difference between the intervention group and the placebo group was statistically significant for all supplements except vitamin C.

According to the food frequency questionnaires filled out by the participants before and after the study, 20 patients used other supplements at the start of the study, and 10 of these continued to take the supplements during the study. Intake of vitamin E, selenium and vitamin C from foods did not change significantly in the intervention or placebo group during the study.

In Table 3 the effects of the intervention on serum levels of PSA are shown. Geometrical means of serum levels of PSA in the intervention group were 11.3 [95%CI: 9.0–14.2] μg/l at baseline and 14.4 [95%CI: 11.5–18.1] μg/l post-intervention, i.e. an increase by 1.3 [1.2–1.4] μg/l. In the placebo group, PSA was 12.2 [95%CI: 9.9–15.1] μg/l before the study and 13.4 [95%CI: 9.8–18.2] μg/l after the study, i.e. an increase by 1.1 [0.9–1.4] μg/l. The difference in PSA change during the study between the intervention and placebo groups was not statistically significant (p = 0.67).

Serum values of testosterone, DHT, LH and SHBG before and after intervention are shown in Table 4. In the intervention group and in the placebo group, plasma levels of these hormones did not change significantly during the study. No significant difference between the intervention and placebo groups was observed in change in plasma levels of testosterone (p = 0.28), DHT (p = 0.72), LH (p = 0.91) or SHBG (p = 0.20).

Haemoglobin and alkaline phosphatase levels remained unchanged during the study period.
4. Discussion

The incidence of latent prostate cancer is almost identical all over the world, but the incidence of its clinical malignant state is much higher in Western than in Eastern countries. Dietary and environmental factors are thought to play a role in the progression of a tumour from its latent into its clinical phase. If certain dietary factors and supplements delay tumour progression in the latent phase, it is not unlikely that they may also be effective in delaying tumour progression in an established tumour.

The aim of the present study was to test the effect of a combination of vitamin E, selenium, vitamin C and coenzyme Q10 in patients with hormonally untreated carcinoma of the prostate and rising serum levels of PSA. In addition, we wanted to test the effect of these supplements on serum testosterone, DHT, LH and SHBG. We chose these supplements, based on the literature, as promising candidates to influence prostate tumour progression, and because of a potential synergistic effect of these compounds in a mixed supplement.

Vitamin E, an important antioxidant, plays a role in immunocompetence, inhibition of mutagen formation, repair of membranes and DNA, and blocking of nitrosamine formation. Because of the probable association between these functions and inhibition of carcinogenesis, it has been suggested that vitamin E may be useful in cancer prevention. Several epidemiological studies have correlated serum vitamin E levels with prostate cancer mortality [4,17]. Supplementation with vitamin E reduced all stages of prostate cancer incidence with 32% and mortality from prostate cancer by 41% [5].

Selenium is an essential trace-nutrient and is critical for the activity of glutathione peroxidase, which may protect DNA and other cellular molecules against oxidative damage. At relatively high levels, selenium protects against the action of certain carcinogens in various animal models. When present in high doses, selenium has also been shown to suppress cell proliferation and enhance immune response, thus functioning similarly to vitamin E. An additional function of selenium is to spare vitamin E.

In a human trial, supplementation of subjects with selenized yeast was reported to induce a 63% reduction in prostate cancer incidence, compared to placebo controls [6]. Although this was a secondary finding, these results did suggest that selenium may be useful in the prevention of prostate cancer. In several prospective cohort studies, men with toenail selenium level had a 50–60% reduction of risk for advanced prostate cancer [18]. Finally, Cho et al. found that methylselenol or its precursor methylseleninic acid specifically and rapidly inhibit PSA expression in-vitro. Two mechanisms of action are described: inducing PSA protein degradation and suppressing androgen-stimulated PSA transcription [19]. Selenomethionine, however, did not affect PSA secretion in the rodent LNCaP model, independent of its effect on tumour growth [20]. Changes in serum PSA levels in individual patients during selenium supplementation were not an effect specific for PSA secretion, but rather a useful indicator for changes in disease progression in individual patients [20].

Vitamin C is a strong antioxidant and has shown to inhibit growth of several cultured rodent and human tumor cells, in a concentration-dependent manner [21]. There are no significant intervention studies to date that demonstrate a protective or direct therapeutic effect of vitamin C supplementation against any form of cancer, including prostate cancer. However, vitamin C, vitamin E and other antioxidants were shown to synergistically inhibit tumor growth in vivo [21].

Coenzyme Q10 is a strong antioxidant and has been shown to have both anti-cancer and immune enhancing properties when tested in animals [22].

In patients with recurrent prostate cancer who received 600 mg coenzyme Q10 daily, a stabilization

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Table 4

<table>
<thead>
<tr>
<th>Serum concentrations</th>
<th>Group</th>
<th>Number of patients</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydrotestosterone (nmol/l) Verum</td>
<td>13</td>
<td>1.4 [1.1–1.8]</td>
<td>1.5 [1.1–1.9]</td>
<td>0.1 [–0.1–0.2]</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11</td>
<td>1.4 [1.0–1.9]</td>
<td>1.9 [1.1–2.7]</td>
<td>0.5 [0.3–0.6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteinising Hormone (U/l) Verum</td>
<td>26</td>
<td>9 [6–12]</td>
<td>7 [5–9]</td>
<td>2 [–5–1]</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Sex Hormone Binding Globulin (nmol/l) Verum</td>
<td>27</td>
<td>48 [42–55]</td>
<td>44 [37–51]</td>
<td>4 [–6–(–1)]</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

Values represent means [95% confidence intervals], and p-values refer to the difference in change between the verum and placebo group.
of PSA in 60 days was seen. At 360 days, the PSA and prostate volume were reduced by 73 and 48%, respectively [11]. None of the cancer studies on coenzyme Q10 reported to date have been designed as clinical trials with adequate controls and randomization. Therefore no conclusions as to the true efficacy of coenzyme Q10 therapy can be drawn.

We also expected a positive outcome of our study, because an earlier randomised clinical intervention study [10] showed a PSA response already after six weeks of intervention with a mixed supplement in 37 men. We expected that our study, with a larger number of patients and a longer intervention period would also show a significant PSA response in the intervention group.

Based on the results mentioned above we expected that the mixed supplement used in our study would result in a PSA response.

We found, however, no significant differences in the changes of serum levels of PSA and hormones between the intervention group and the placebo group during the study. How can the negative outcome of this study be explained?

Our results cannot exclude the possibility that, despite the lack of effect on serum levels of PSA, the supplements in our study could have had an effect on the tumour by a different mode of action, which does not affect PSA levels. Although PSA is considered a valid surrogate endpoint for prostate cancer progression, it has not been validated to measure the effects of nutritional supplements in chemoprevention or as a treatment of prostate cancer progression. In fact, it has been argued that, even once validated, PSA as a surrogate endpoint for one supplement may not be a valid endpoint for another supplement [3].

The variability of PSA levels is determined by a biological and an analytical component. To reduce the within-subject variability, serum levels of PSA were measured three times both at baseline and at the end of the intervention period at weekly intervals and the average of the three measurements was used for data analyses. By doing so the standard error in this study was reduced from 9% to ≈5%. The determination of all serum levels of PSA in one central laboratory eliminated the analytical variability. It is therefore unlikely that the variability of PSA could have influenced the results of this study.

Power calculations showed that a minimum number of 60 patients should have been sufficient to detect a 5% (i.e. 0.6 μg/l) difference in change of PSA baseline values between the placebo group and the serum group over the study period. In view of our findings, it is very unlikely that a larger number of subjects would have altered the results of this study.

Compliance in our study, as checked by counting the remaining supplements at the end of the study and by measuring the plasma levels of the supplements at the beginning and the end of the study, appeared to be excellent. Also, plasma values of the vitamins in the placebo group indicated a good compliance in the intervention group, and at the same time did not give any indication for increased use of supplements in the control group.

It could be argued that the intervention period of this study might have been too short to allow an effect on serum levels of PSA. This explanation, however, would seem less likely in view of an earlier cross-over study in only 37 men, which showed borderline significant results of a nutritional supplement after an intervention period of only 6 weeks [8].

Since we used mixed supplements in this study, the effects of one supplement could also have been inhibited by one of the other supplements. However, this possibility would appear unlikely since the available literature suggests that the combination of vitamin C, selenium and vitamin E may in fact show synergistic effects in inhibiting tumour growth [11,12].

The dose of supplements used in this study was considerably higher than the consumption of vitamin C, vitamin E, selenium and coenzyme Q10 in the average western diet. An even higher dosage than used in the present study might cause adverse effects. By way of precaution, the study subjects were asked during every consultation whether they had experienced any adverse effects, and no adverse effects were reported.

A model of tertiary prevention has been used in this study in order to appraise the potential of vitamin E, selenium, vitamin C and coenzyme Q10 in inhibiting tumour progression. The patients in our study had a histological proven prostate cancer with rising serum levels of PSA, and were either being controlled by a ‘wait and see’ policy or had rising serum levels of PSA after treatment with radical intent. The advantage of this model is a well-defined endpoint (i.e. PSA level). Naturally, the extrapolation of this model to primary prevention is not straightforward. Thus, if a supplement does not inhibit further progression of a clinically advanced stage of prostate cancer, this does not necessarily preclude its use as a primary preventative agent.

In conclusion, we found no effect of a mixed high dose supplement of vitamin E, selenium, vitamin C and coenzyme Q10 on serum levels of PSA, testosterone, DHT, LH or SHBG in patients with prostate cancer and rising serum levels of PSA, despite increasing plasma levels of vitamin E, selenium and coenzyme Q10.
Acknowledgements

We acknowledge the financial support of AstraZeneca, Zoetermeer, Netherlands, the Comprehensive Cancer Centre Limburg, Maastricht, The Netherlands; and Pharma Nord, Copenhagen, Denmark, who also provided us with the supplements and placebos for the present study.

References

[10] Judy WV, Willis RA, Folkers K. Regression of prostate cancer and pharmacological and dietary antioxidants, scavenging free oxygen radicals, and reducing the rate of oxidative stress and genetic mutations. They also induce cell cycle arrest. They do not induce apoptosis to any significant degree. Cells which have been induced to stop proliferating may still continue to secrete PSA into the serum. While PSA is a reasonable surrogate marker for response to a therapy levels of the micronutrients did increase. The authors should be congratulated for carrying out a randomized trial in this setting.

The lack of PSA response is not surprising. The micronutrients used acted in several ways. They act as anti-oxidants, scavenging free oxygen radicals, and reducing the rate of oxidative stress and genetic mutations. They also induce cell cycle arrest. They do not induce apoptosis to any significant degree. Cells which have been induced to stop proliferating may still continue to secrete PSA into the serum. While PSA is a reasonable surrogate marker for response to a therapy

Editorial comment

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This paper represents an important contribution to the literature on the role of micronutrients in prostate cancer prevention and treatment. 70 patients with biochemical recurrence of prostate cancer were randomized between vitamin E, selenium, vitamin C, and coenzyme Q10, or placebo, for 21 weeks. The study found no difference in PSA response or androgen levels between the treatment and control groups. Serum levels of the micronutrients did increase. The authors should be congratulated for carrying out a randomized trial in this setting.

The lack of PSA response is not surprising. The micronutrients used act in several ways. They act as anti-oxidants, scavenging free oxygen radicals, and reducing the rate of oxidative stress and genetic mutations. They also induce cell cycle arrest. They do not induce apoptosis to any significant degree. Cells which have been induced to stop proliferating may still continue to secrete PSA into the serum. While PSA is a reasonable surrogate marker for response to a therapy
designed to reduce prostate cancer cell number, it may not be a useful marker for a treatment which is primarily mediated by cell cycle arrest. While arrested cells eventually die, this may be a prolonged process, taking several years. 21 weeks of treatment may not have been long enough to observe a response.

It is also possible that these micronutrients may be effective at inhibiting the proliferation of microfoci of prostate cancer, and ineffective at treating more advanced disease. The median PSA at baseline was 11–12 ng/ml; in the post-prostatectomy setting, this represents a moderately substantial volume of disease. A significant proportion of these patients may have had occult bone metastases. Paracrine factors in bone marrow could overwhelm the inhibitory effects of micronutrients.

The benefit of vitamin E and selenium in prostate cancer prevention will eventually be decided by the SELECT trial in 31,000 patients followed for 12 years. This drastically smaller study makes an important contribution, however. Patients with established biochemical recurrence can be counseled that these micronutrients are unlikely to have a measurable effect on their PSA in a 5–6 month period.

A study involving a much longer duration of therapy, i.e. 2–3 years, would be worth doing.