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Prostate-Specific Antigen Modulatory Effect of a Fermented Soy Supplement for Patients with an Elevated Risk of Prostate Cancer: a Non-Randomized, Retrospective Observational Registration

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Key Words

Prostate • Prostate biopsy • Prostate cancer detection • Prostate specific antigen • Phytotherapeutics

Abstract

Objective: To investigate the efficacy of a 6-month fermented soy supplement (equol-containing), measured by prostate-specific antigen (PSA) stabilization or PSA decrease from baseline (PSA modulatory effect) in men with an elevated risk of prostate cancer (PCa), with a WHO performance 0–2 and a follow-up of 12 months. ***Methods:*** The patient population consisted of men with an elevated risk of PCa and a prior negative prostate biopsy within 1 year from starting therapy. Serum PSA values were recorded at inclusion (iPSA), at 6 months (1PSA), and optionally at 12 months (2PSA). Statistical analysis was carried out using the Wilcoxon rank sum test ($p < 0.05$). ***Results:*** In total, 137 men used fermented soy for any prostatic reason. After inclusion criteria for an elevated risk of PCa and a prior negative prostate biopsy, we selected 58 patients. Among these, there was a significant PSA modulatory effect (iPSA–1PSA, $p = 0.003$). This modulatory effect was more strongly evident in the subgroup of patients with an elevated iPSA (≥ 4 ng/ml) (n = 33, iPSA–1PSA, $p = 0.003$, iPSA–2PSA, $p = 0.002$). ***Conclusions:*** We demonstrated a significant PSA modulatory effect of a 6-month fermented soy supplement in men with an elevated risk of PCa and a prior negative prostate biopsy. This positive effect is currently being investigated in a prospective study. Further evaluation of the role of fermented soy supplements is warranted in a preventive and therapeutic setting of men at an elevated risk of PCa.

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Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men worldwide with an estimated 1.1 million new cases in 2012 with almost 70% (759,000) of them occurring in more developed regions [1]. The incidence rate of PCa is much lower in Asian than in Western populations, especially in Eastern and South-Central Asia [1]. However, Asian migrants to the United States have a higher PCa incidence when they adopt a Western diet [2–4]. Similarly, PCa incidence and mortality

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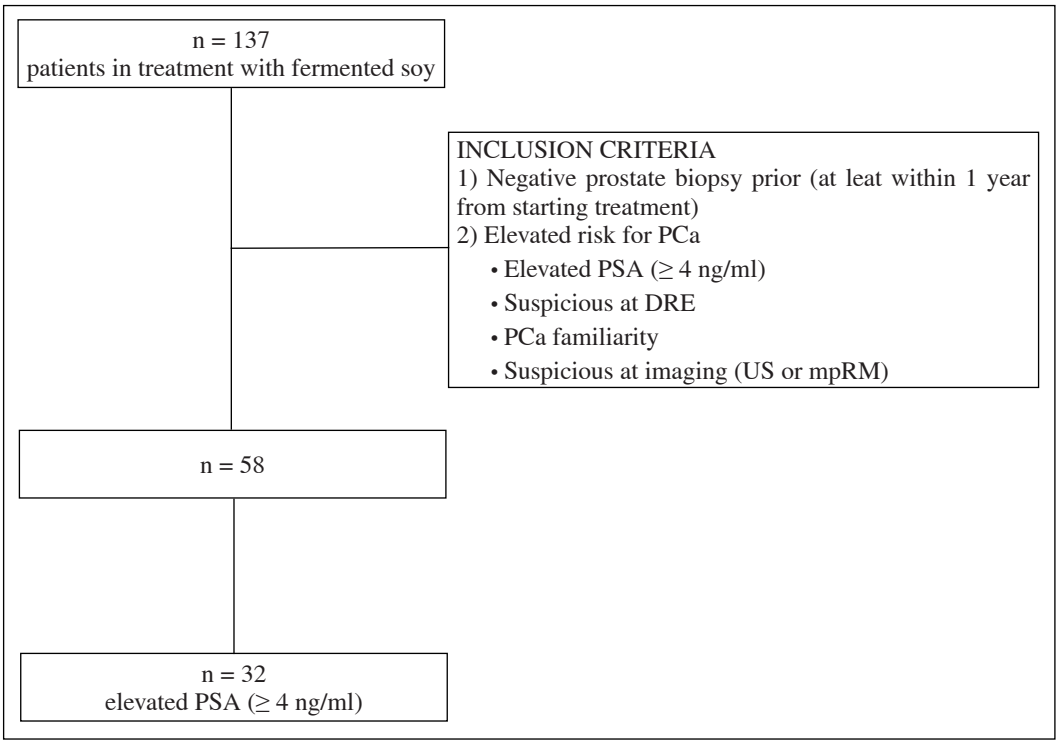

Fig. 1. Retrospective registration study investigating the effect of a fermented soy supplement in men with an elevated risk of prostate cancer and a prior negative prostate biopsy. Inclusion criteria are provided in the figure. In total, 58 patients were included of which 32 had an elevated PSA > 4 ng/ml.

has increased in Asian countries simultaneously with the westernization of their diet [5]. Therefore, environmental factors such as dietary habits have been presumed to play an important role in prostate carcinogenesis.

Soy foods, commonly consumed in Asian countries, are a rich source of isoflavones which possess anticancer activities. The mean isoflavone intake in Asian countries is approximately 50 mg daily, which is about 10 times higher than in Western countries [5, 6]. Epidemiological studies showed that soy/isoflavones consumption in Asian populations is associated with a decrease in PCa risk [6]. Randomized controlled trials suggested there may be support for the epidemiological findings of a potential role for soy/soy isoflavones in PCa risk reduction. A good safety profile was also demonstrated for soy/soy isoflavones supplementation [7].

However, there is no clear understanding of the impact of soy/soy isoflavones on prostate-specific antigen (PSA) in men with, or at an identified risk of PCa [6–8]. During the past years we have conducted a small open-label study demonstrating a decrease or stabilization of PSA in men diagnosed with isolated high-grade prostatic intraepithelial neoplasia on biopsy in response to a 6-month dietary supplementation consisting of selenium, vitamin E, and soy isoflavones. It was shown in this study that a decrease in the PSA level while being on the supplement predicted a significantly lower risk of PCa in future biopsies [9].

The main isoflavones found in most soy foods are genistein, daidzein, and glycitein. Daidzein is converted to equol by the intestinal microflora of certain individuals [10]. Equol is 10 times more biologically potent than daidzein in delaying PCa growth [11]. The exact mechanism by which isoflavones and more specifically equol may prevent the development or progression of PCa remains unclear [12–14]. The efficacy of soy isoflavones appears to be a function of the individual's ability to produce equol [12, 15]. Only 20–35% of Western adult populations host the intestinal bacteria that convert daidzein to equol [10]. Fermentation of soybeans results in extensive biotransformation of isoflavones with a significant increase in production of equol from daidzein. A possible strategy to increase the equol production is by changing the intestinal flora and changing non-equol producers to producers. A newly identified equol-producing bacterium was recently isolated from human fe-

ces of Japanese adults and further research is ongoing [16, 17]. Nevertheless, the easiest way is to change the diet by adding nutrients such as fermented soy (equol) in the form of a supplement. PraëCell® is a unique and patented supplement based on specific soybeans (ZhenHua) from the Chinese highlands fermented by a unique strain of bacteria [18]. Consumption of dietary supplements is an interesting approach in PCa as non-invasive active surveillance has increased in popularity as a strategy for reducing potential overtreatment of this slow-growing but potentially fatal disease.

Considering all of the above and starting from the experience of our last study [9], we hypothesized that the intake of a fermented soy supplement by patients with an elevated PCa risk might modulate PSA and help to select out the population at real increased risk of having occult PCa. Such preventive strategy has many advantages, as it is easy to use, non-invasive, non-toxic (and well tolerated), and not expensive. This retrospective study investigated the effect of a 6-month dietary supplement with fermented soy as the main component on the PSA level in 58 men with an elevated risk of PCa and a prior negative prostate biopsy.

Materials and Methods

Subjects

A group of 137 patients received fermented soy for any prostatic disease between November 4th, 2013 and April 21st, 2016. We included in the analysis only patients with an elevated risk of PCa and with a negative prostate biopsy performed within 12 months from starting treatment. An elevated risk of PCa was defined by any one of the following criteria: PSA > 4 ng/ml, PSA density > 0.15 ng/ml/ml, PSA velocity > 0.75 ng/ml/y, suspect lesion at digital rectal examination (DRE), suspect lesion at transrectal ultrasound (TRUS)/magnetic resonance imaging (MRI), and family history of PCa. Patients with a lower performance status and those with a known history of soy allergy were excluded. Patients were included when they had a follow-up of at least 6 months [median 11 months, interquartile range (IQR): 7.5–17 months]. Data were acquired at 6, 12, and 18 months.

Fermented Soy Supplement

All patients were given PraëCell® (Health, Science & Nutrition, Antwerp, Belgium), 1 capsule per day for at least 6 months. Praëcell® is a commercially available, dietary supplement therapy consisting of fermented soy (ZhenHua) (60 mg), isoflavones (10 mg), vitamin C (90 mg), beta-glucan (105 mg), lycopene (3 mg), vitamin D (5 µg), zinc (5 mg), and selenium (27.5 µg) per capsule.

Study Design and Endpoint

This paper presents the results of a 6-month, non-randomized, open-label, retrospective registration study investigating the effect of a fermented soy supplement in men with an elevated risk of PCa and a prior negative prostate biopsy (fig.1). The endpoint of this trial was the efficacy of a fermented soy supplement, measured by PSA stabilization or PSA decrease from the baseline (PSA modulatory effect).

Measurements

At the baseline, at 6 months, and optionally at 12 months, blood samples were obtained for PSA measurement. A DRE was performed at baseline and all follow-up visits. TRUS or multiparametric MRI and an estimation of prostate volume were performed at baseline and were optional at follow-up visits. TRUS-guided needle biopsy was performed within 12 months from starting treatment.

Statistical Analysis

Principles of descriptive statistics were used to report patient characteristics at the baseline, technical imaging was used and histological specimens after biopsy with relative percentages and median with IQR according to the values. Statistical analysis were carried out using the Wilcoxon rank sum test to evaluate the assumption that fermented soy changes the serum PSA with statistical significance ($p < 0.05$). Graphics with boxplots illustrate the results in changing PSA. Data were analyzed using the statistical software R version 3.3.2.

Results

In total, 137 men used fermented soy for any prostatic reason. After inclusion criteria for an elevated risk of PCa and a prior negative prostate biopsy, we selected 58 patients. Their median age was 68 years (IQR: 58–73 years). Median follow-up was 11 months. Descriptive statistics are presented in table 1.

Table 2 shows the statistical significance (Wilcoxon rank sum test) of the PSA measured at the first control (iPSA–1PSA) and PSA measured at the second control (iPSA–2PSA) after fermented soy supplementation compared with the initial PSA at inclusion. For the subgroup of patients with an elevated PSA, the statistical significance of the 2PSA compared to the 1PSA (1PSA–2PSA) is also reported.

The 1PSA modulatory effect compared with the initial PSA values at inclusion reached statistical significance in the study group of patients with an elevated risk of PCa and a prior negative prostate biopsy (n = 58) (iPSA–1PSA, p = 0.003) (fig. 2). The 1PSA and 2PSA modulatory effect compared with the initial PSA values at inclusion reached statistical significance in the subgroup of patients with an elevated PSA (n = 33) (iPSA–1PSA, p = 0.003, iPSA–2PSA, p = 0.002) (fig. 3).The PSA modulatory effect of the fermented soy supplement was more strongly evident in the subgroup of patients with an elevated iPSA.

Table 1. Descriptive statistics for patients treated with a fermented soy supplement between November 2013 and April 2016 at a single center

	Values
Patient characteristics	
Total, n	58
Median age (IQR), years	68 (58–73)
Median prostate volume (IQR), ml	20 (15–35)
Positive familiarity, n (%)	4 (6.9)
DRE	
Normal, n (%)	24 (41.4)
Hardness, n (%)	4 (6.9)
Benign prostatic hyperplasia, n (%)	21 (36.2)
Prostatitis, n (%)	2 (3.4)
Imaging	
Ultrasound suspicious area or multiparametric MRI, n (%)	10 (17.2)
Normal, n (%)	9 (15.5)
PCa, n (%)	3 (5.2)
Doubt, n (%)	7 (12.1)
Prostatitis, n (%)	1 (1.7)
PIRADS 4–5, n (%)	4 (6.9)
Median follow-up (IQR), months	11 (7.5–17)

PIRADS = Prostate Imaging Reporting and Data System.

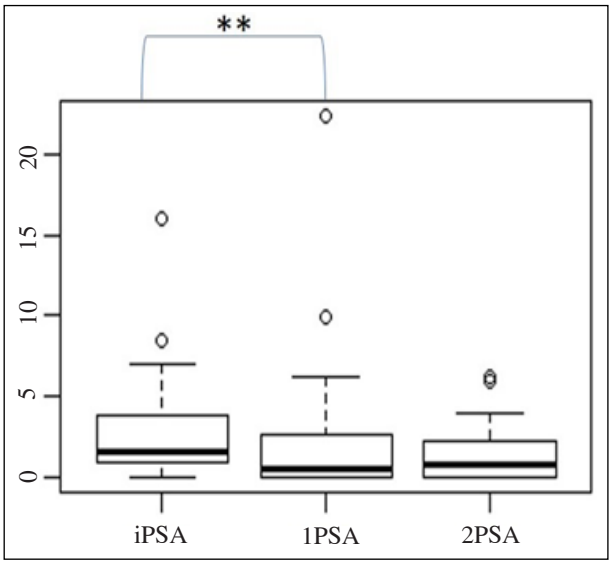

Fig. 2. PSA modulatory effect of a fermented soy supplement in patients with an elevated risk of PCa and a prior negative prostate biopsy (n = 58). **The difference between iPSA and 1PSA was statistically significant (iPSA–1PSA, p = 0.003).

Table 2. Wilcoxon rank sum test for analyzing the PSA modulatory effect of a 6-month fermented soy supplement in patients with elevated risk of PCa ($p < 0.05$)

	n	p
Number of PCa, prior negative prostate biopsy	58	
iPSA–1PSA		0.003
iPSA–2PSA		0.125
Elevated PSA (≥ 4 ng/ml), prior negative prostate biopsy	33	
iPSA–1PSA		0.003
iPSA–2PSA		0.002
1PSA–2PSA		0.52

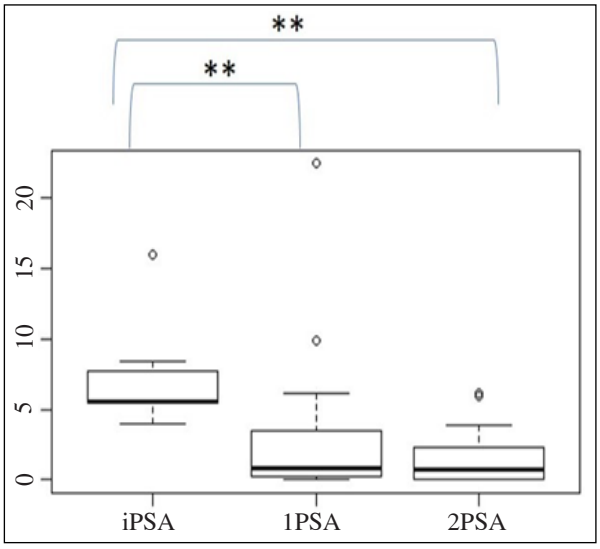

Fig. 3. PSA modulatory effect of a fermented soy supplement in patients with an elevated risk of PCa, a prior negative prostate biopsy and elevated PSA (≥ 4 ng/ml) (n=32). **The difference between iPSA-1PSA and iPSA-2PSA was statistically significant (iPSA–1PSA, p = 0.003; iPSA-2PSA, p=0.002).

Figure 4 and 5 present the decrease of the PSA value during consumption of the fermented soy supplement in the study group (n = 58) and in the subgroup (n = 33), respectively.

Discussion

Our study has shown that in men with an elevated PCa risk and a prior negative prostate biopsy, the PSA level remained stable or decreased from the baseline while being on a fermented soy supplement for 6 months. This finding is interesting, because several studies had not been able to show a reduction in PSA while on a soy diet or soy isoflavones supplement. Shortcomings of many studies published to date were small patient numbers,

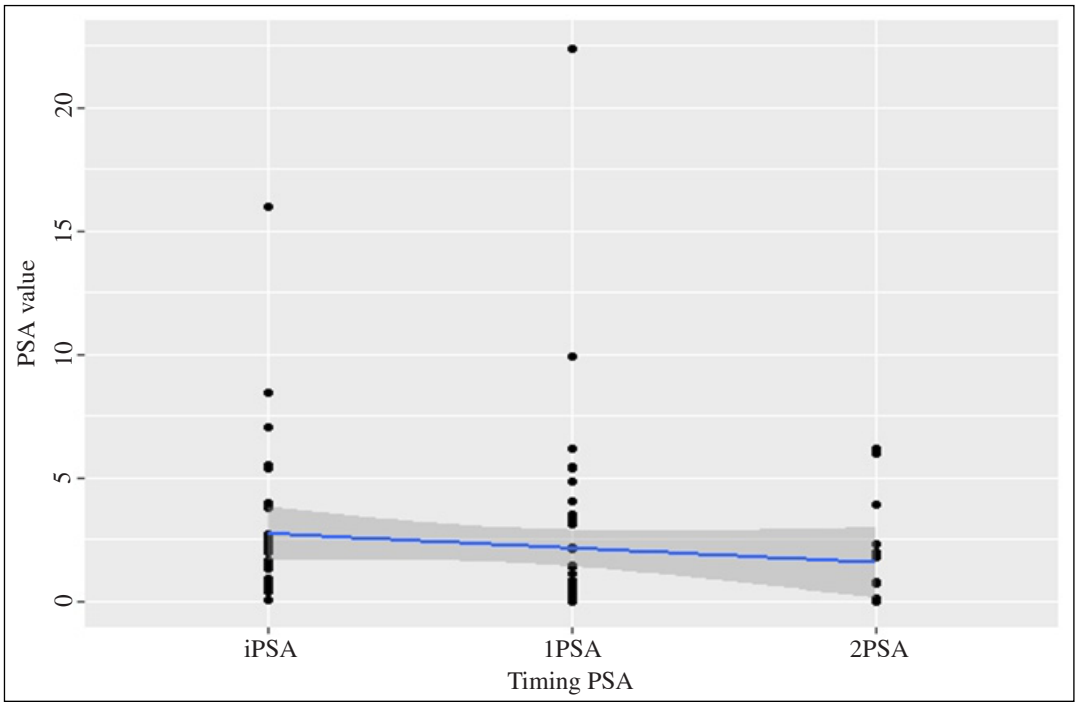

Fig. 4. Decrease of the PSA value during consumption of the fermented soy supplement in patients with an elevated risk of PCa and a prior negative prostate biopsy (n = 58).

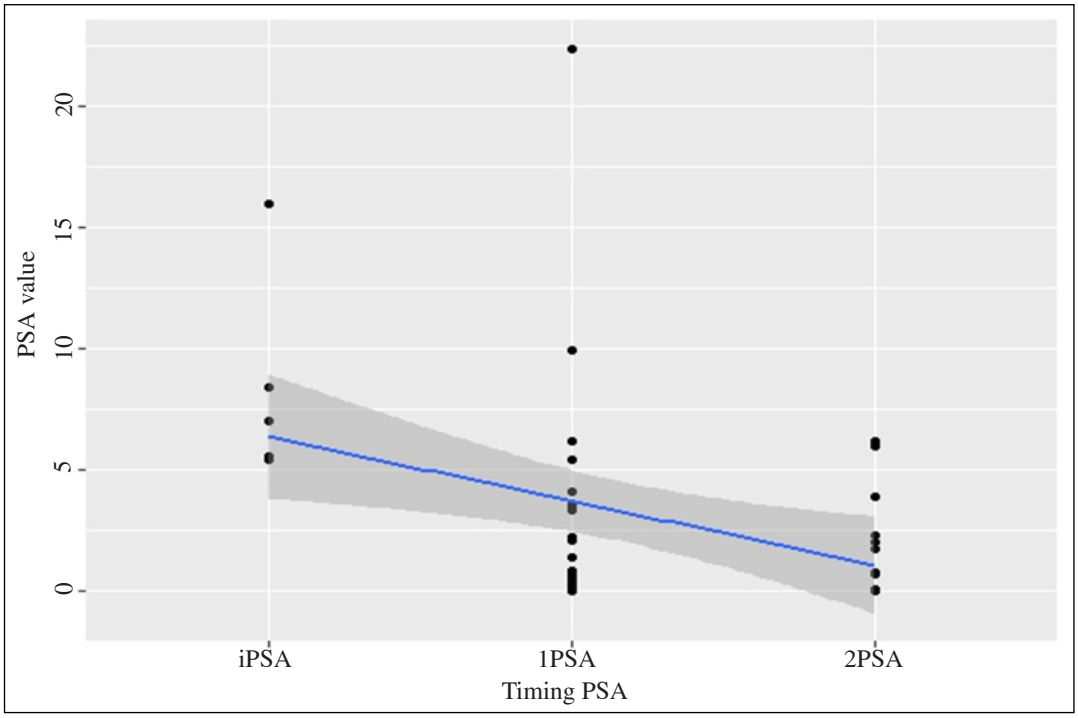

Fig. 5. Decrease of the PSA value during consumption of the fermented soy supplement in patients with an elevated risk of PCa, a prior negative prostate biopsy and elevated PSA (≥ 4 ng/ml) (n = 32).

lack of randomization, short-term isoflavone administration, possibly insufficient doses, the variety of forms in which isoflavones were administered, and the heterogeneity of dosage regimens and study populations.

Eight randomized controlled trials (RCT) were conducted to evaluate the efficacy and the safety of soy/soy isoflavones in men with histologically confirmed PCa (6 RCTs) or with a clinically identified risk of PCa (2 RCTs) [7]. A meta-analysis of the 2 RCTs investigating the development of PCa in men with a clinically identified risk [19, 20] showed a statistically significant reduction in PCa diagnosis after the administration of soy/soy isoflavones (relative risk = 0.49, 95% confidence interval 0.26–0.95) [7]. An individual Japanese RCT of 158 men with serum PSA levels of 2.5–10.0 ng/ml, and a single, negative prostate biopsy within 12 months prior to enrolment, showed a significant lower incidence of PCa in the isoflavones group (60 mg/d) compared to the placebo group for 53 patients aged ≥ 65 years (28 vs. 57.1%, p = 0.031). No significant differences in PSA levels within or between groups were observed [19]. The other RCT included 58 patients with high risk for future PCa (high-grade prostatic intraepithelial neoplasia, atypical small acinar proliferation) or low-grade PCa. Less PCa was detected after 6 months of a daily consumption of 40 mg soy protein (107 mg isoflavones). PSA levels did not differ among the groups at 3 and 6 months [20].

Several RCTs and small non-randomized studies investigating soy protein/soy isoflavones supplements that included PSA endpoints were conducted in healthy men, men with PCa undergoing active surveillance, men with untreated localized PCa, and men with an elevated PSA after radical prostatectomy or radiation. A meta-analysis of 7 RCTs [7] that included PSA endpoints showed no statistically significant effect on PSA levels in men with PCa [21–25], or who were at risk of PCa [19, 20]. However, in two individual RCTs, the decrease in PSA was significant [25] or approached significance [21]. In the first RCT, the PSA and the free/total PSA ratio were favorably influenced in men consuming bread high in heat-treated soy grits (change in PSA level; -12.7% for soy grits vs. 40% for wheat, p = 0.02) [25]. In the second RCT, daily consumption of 30 mg genistein for 3–6 weeks prior to prostatectomy reduced serum PSA levels in patients with localized PCa. PSA decreased by 7.8% in the genistein arm and increased by 4.4% in the placebo arm (p = 0.051) [21]. In addition, Kumar et al. [23] showed that in a group of early PCa patients (Gleason score 6 or less), the serum total PSA decreased or was unchanged in 69% of the patients treated with isoflavones (60 mg) compared to 55% in the placebo group. In 19% of patients receiving soy isoflavones, the serum total PSA was reduced by ≥ 2 points during the intervention period. Moreover, Hussain et al. [26] showed that although soy isoflavones supplements did not provoke sustained decreases in PSA, stabilization of the PSA occurred in 83% of hormone-sensitive PCa patients and 35% of hormone-refractory PCa patients. In a more recent RCT, daily consumption of a 20 mg soy protein isolate supplement for 24 months did not reduce biochemical recurrence of PCa after radical prostatectomy [27].

An important difference between our study and previous studies was the use of fermented soy (equol) as the main substance of our dietary supplement in patients with an elevated risk of PCa. Equol which is metabolized from daidzein by certain human intestinal bacteria, is biologically more active in delaying PCa growth than any other isoflavone aglycone [11]. A case-control study showed that the percentage of equol producers in patients with PCa was significantly lower than in healthy controls (30.3 vs. 49.5%, p = 0.013) [28]. Our analysis demonstrated several important findings. In the group of patients with an elevated risk of PCa and a prior negative prostate biopsy, the PSA modulatory effect reached significance, at the first control after starting treatment with the fermented soy supplement. The most remarkable findings were observed in the subgroup of patients with an elevated PSA (≥ 4 ng/ml). In this subgroup, the PSA modulatory effect at the first and second control after starting treatment with the fermented soy supplement reached statistical significance, compared with the initial PSA values at inclusion.

The current study is not devoid of limitations. First, our findings must be interpreted with all the limitations related to retrospective studies. Second, our conclusions are based on group analyses with small sample sizes.

Further well-designed studies are warranted to determine the positive effect of the fermented soy supplement on PSA levels and PCa risk. A prospective study is designed by our department to fully investigate the effectiveness of fermented soy supplement intake, measured by the PSA modulatory effect, in patients with an elevated risk of PCa and prior negative prostate biopsies. The protocol of this prospective study was approved by the Ethics Committee of the University Hospital KU Leuven on March the 3rd, 2017. If this prospective study confirms the PSA-modulatory effect of a fermented soy supplement (stabilize or decrease PSA) in patients with an elevated PCa risk, prescribing such supplement can help the urologist to select out the patients at real in-

creased risk of having occult PCa. When the PSA level increases from the baseline during fermented soy consumption, additional prostate biopsies remain necessary and adequate treatment may be needed.

Conclusions

In this study, we demonstrated a significant PSA modulatory effect of a 6-month intake of a fermented soy supplement in men with an elevated risk of PCa and a prior negative prostate biopsy. This modulatory effect was more strongly evident in the subgroup of patients with an elevated PSA (≥ 4 ng/ml). The positive effect of a fermented soy supplement is currently being investigated in a prospective study. Further evaluation of the role of fermented soy supplements is warranted in the preventive and therapeutic setting of men with an elevated risk of PCa.

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