# Association between selenium and lycopene supplementation and incidence of prostate cancer: Results from the procomb trial


# Association between Selenium and Lycopene supplementation and incidence of prostate cancer: results from the post-hoc analysis of the Procomb trial.

Giuseppe Morgia , Salvatore Voce , Fabiano Palmieri , Marcello Gentile , Gennaro Iapicca , Antonella Giannantoni , Franco Blefari , Marco Carini , Giuseppe Vespasiani , Giorgio Santelli , Salvatore Arnone , Rosaria M. Pareo , Giorgio Ivan Russo

PII: S0944-7113(17)30083-1
DOI: 10.1016/j.phymed.2017.06.008
Reference: PHYMED 52213

To appear in: *Phytomedicine*

Received date: 9 April 2017
Revised date: 23 May 2017
Accepted date: 17 June 2017

Please cite this article as: Giuseppe Morgia , Salvatore Voce , Fabiano Palmieri , Marcello Gentile , Gennaro Iapicca , Antonella Giannantoni , Franco Blefari , Marco Carini , Giuseppe Vespasiani , Giorgio Santelli , Salvatore Arnone , Rosaria M. Pareo , Giorgio Ivan Russo , Association between Selenium and Lycopene supplementation and incidence of prostate cancer: results from the post-hoc analysis of the Procomb trial., *Phytomedicine* (2017), doi: 10.1016/j.phymed.2017.06.008

# Association between Selenium and Lycopene supplementation and incidence of prostate cancer: results from the post-hoc analysis of the Procomb trial.

Giuseppe Morgia[a], Salvatore Voce[b], Fabiano Palmieri[b], Marcello Gentile[c], Gennaro Iapicca[c], Antonella Giannantoni[d], Franco Blefari[e], Marco Carini[f], Giuseppe Vespasiani[g], Giorgio Santelli[h], Salvatore Arnone[i], Rosaria M. Pareo[j]; Giorgio Ivan Russo[a,*]

[a]Department of Urology, University of Catania, Catania, Italy
[b]Urologic Unit, Lugo of Romagna Division, Ravenna, Italy
[c]Urologic Unit, Avellino Division, Avellino, Italy
[d] Department of Urology and Andrology, University of Perugia, Perugia, Italy
[e] Urologic Unit, Misericordia e Dolce Hospital, Prato, Italy
[f] Department of Urology, Careggi Hospital, University of Florence, Florence, Italy.
[g] Department of Urology, University of Tor Vergata, Rome, Italy
[h] Urologic Unit, Lucca Division, Lucca, Italy
[i] Urologic Unit, Ravenna Division, Ravenna, Italy
[j] Urologic Unit, Regina Margherita Hospital, Rome, Italy

*Corresponding author:*
*Dr. Giorgio Ivan Russo, M.D.*
Department of Urology, University of Catania
Tel. +39 (95) 3782712 Fax +39 (95) 3782373
*E-mail address:* giorgioivan@virgilio.it

## ABSTRACT

*Background:* Many potential chemopreventive agents have been used in PCa prevention, including selenium (Se) and lycopene (Ly). However, their role has been matter of debate over the years, due to potential of promotion of PCa.

*Purpose:* In this study we aimed at evaluating the incidence risk of prostate cancer (PCa) in a cohort of patients treated with Se and Ly.

*Methods:* The Procomb trial design has been previously published (ISRCTN78639965). From April 2012 to April 2014 209 patients were followed and underwent prostate biopsy when PSA ≥4 ng/ml and/or suspicion of PCa. The all cohort was composed by patients treated with Se and Ly (Group A = 134 patients) and control (Group B = 75 patients).

*Results:* During the follow-up time of 2 years, a total of 24 patients (11.5%) underwent prostate biopsy, of which 9 (4.3%) where diagnosed with PCa and 15 (7.2%) where diagnosed with benign prostatic hyperplasia. We did not observe statistical differences in terms of mean changes of PSA between the two groups (p-value for trend = 0.33). The relative risk (RR) for PCa was 1.07 and 0.89 in group A and B, respectively (p = 0.95). At the multivariate Cox regression analysis supplementation with Se and Ly was not associated with greater risk of PCa (hazard ratio: 1.38; p = 0.67).

*Conclusion:* In this analysis we did not show evidences supporting a detrimental role of Selenium and Lycopene supplementation in increasing PCa after 2 years of therapy, nor supporting a protective role.

**Trial registration:** ISRCTN ISRCTN78639965, Registered 06 November 2013. Retrospectively registered.

*Keywords:* Prostate cancer; Selenium; Lycopene; Prevention

*Abbreviations:*

PCa = prostate cancer, Se = Selenium, Ly = Lycopene, PSA = prostate specific antigen, RR = relative risk, HGPIN = high grade prostatic intraepithelial neoplasia (HGPIN), PIN = prostatic intraepithelial neoplasia, ASAP = atypical small acinar proliferation, Lower urinary tract symptoms = LUTS, Hazard ratio = HR, GTC = green tea catechins

## Introduction

Prostate cancer (PCa) has always been considered as an ideal target for chemoprevention thanks to its long natural history and its high incidence (Cantiello et al., 2016; Gasmi and Thomas Sanderson, 2013; Michaelsen et al., 2015; Tsai et al., 2015; Van Poppel and Tombal, 2011). The influence of diet, ethnicity and environmental factors on the development of PCa is well documented by several epidemiological studies (Breslow et al., 1977; Kheirandish and Chinegwundoh, 2011; Klein and Thompson, 2012). For these reasons, over the past decade, many potential chemopreventive agents have been used in PCa prevention, including selenium (Se), lycopene (Ly) and green tea catechins (GTC), due to their antioxidant and anti-proliferative activities (Bettuzzi et al., 2006; Mohanty et al., 2005; Sebastiano et al., 2012). In particular, Se is able to decrease the levels and to inhibit the transcription of the androgenic receptor with a presumed protective action in patients with high-grade PIN (Joniau et al., 2007). These properties, along with a low toxicity, has been considered ideal for its use as chemopreventive agent. However, its application has been dramatically refuted as a result of long-term results of the SELECT study (Nicastro and Dunn, 2013; Ramamoorthy et al., 2015). This study has demonstrated the absence of any benefit in reducing the incidence of PCa with the administration of Se and Vitamin E. In addition, therapy with supplemental selenium in patients already suffering from PCa was able to determine an increase in mortality (Kenfield et al., 2015; Vinceti et al., 2014).

To this regard, a recent study by Gontero et al. has shown that the administration of high doses of Ly, catechins and Se in patients with high grade prostatic intraepithelial neoplasia (PIN) (HGPIN) and/or atypical small acinar proliferation (ASAP) was associated with a higher incidence of PCa at re- biopsy and increased expression of microRNAs implicated in the progression of PCa (Gontero et al., 2015). However, some limitations in the study, such as such as low abundance of samples and the reduced exposure time to these

chemopreventive agents (6 months) arise doubts about the role of these compounds in the development of PCa.

For these reasons, we conducted a post-hoc study from the Procomb clinical trial with the aim of evaluating the risk of developing PCa in the cohort of patients treated with Se and Ly.

**Methods**

The design of the Procomb trial has been previously presented (ISRCTN78639965) (Morgia et al., 2014).

All participants provided written informed consent before enrolment and the study was conducted in accordance with regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996). The study was approved by our Institutional Research Ethics Committee of the Policlinico Hospital of the University of Catania.

From March 2011 to March 2012, 225 patients with lower urinary tract symptoms (LUTS) were enrolled in the study in relation to the following inclusion criteria: age between 55 and 80 years, digital rectal examination negative for PCa, PSA <4 ng/ml, International prostate symptoms score (IPSS) ≥ 12, prostate volume ≤ 60 cc (assessed by ultrasound), peak flow ≤15 ml/s, post-void residual <150 ml. Exclusion criteria were patients with prostate cancer, previ- ous bladder cancer, diabetes mellitus, neurogenic disorders, severe liver disease, history of orthostatic hypotension or syncope, symptomatic urinary tract infection, anti-androgens, antidepressants (neuroleptics, anti cholinergics) therapy, recent treatment with an a blocker (within 1 month) or phytotherapy including saw palmetto extract (within 3 months), previous medical therapy with 5-ARI or surgical treatment for LUTS, patients with catheter or with an episode of acute retention of urine in the last 4 weeks.

Participants were randomized into three treatment arms for the treatment of LUTS, each consisting of 75 patients with enlistment in 1:1:1 ratio into arm A (Serenoa repens 320 mg, Ly and Se [Profluss®] 1 tablet per day for 1 year ), arm B (Tamsulosin 0.4 mg 1 tablet per day for 1 year), arm C (Serenoa repens 320 mg, Ly and Se [Profluss®] 1 tablet per day for 1 year + tamsulosin 0.4 mg 1 tablet per day for 1 year). The following post-hoc study was conducted at the end of the clinical trial and conducted from April 2012 to April 2014. Patients who continued treatment were included in the study. Total PSA and digital rectal examination were repeated annually or when clinically indicated as per standard of therapy. In the event of an increase in PSA tot above 4 ng/ml and/or suspected PCa at the digital rectal. Patients with incomplete data were excluded.

For the post-hoc analysis statistical analysis, patients were divided into two groups: Group A (Ly and Se) and group B (control). Safety data were evaluated by considering adverse events (AEs). Treatment-related adverse events were considered those reported side effects after treatment.

One tablet of Profluss1 consisted of 320mg of supercritical CO2 lipidic extract SeR containing 85% of fatty acids sterols, selenium (50mcg) and lycopene (5mg) (Ayanda AS, Norway) and distributed by Konpharma Srl (Rome, Italy).

*Statistical analysis*

The design of the study has been previously showed. The efficacy variables were tested using the Mann-Whitney U test. Quantitative variables were tested using the chi- square test or the Fisher's exact test. The Cochran-Armitage trend test was used to describe the temporal changes of the PSA during follow -up. The relative risk of having Pca was calculated by dividing group A and group B incidence by the general population incidence. The cox regression analysis adjusted for confounding factors (age, PSA, family history of

prostate cancer and number of cores at prostate biopsy) was performed to retrieve the hazard ratio (HR) in order to test the association between Se and Ly supplementation and PCa risk.

**Results**

After the post-hoc analysis, 209 patients with complete data, 134 in group A and 75 in group B were included (Fig. 1). In the Group B no one assumed therapy with Ly and Se. The baseline characteristics of the patients are shown in Table 1. During the 2 years of follow-up, 24 patients (11.5%) underwent prostate biopsy and of these, 9 (4.3%) received a diagnosis of PCa and 15 (7.2%) received a diagnosis of BPH.

There were no significant differences regarding the mean changes of the PSA between the two treatment groups (p-value for trend = 0.33) (Fig. 2). In group A, 9 patients (6.7%) received a diagnosis of BPH, 5 patients (3.7%) of PCa Gleason 6 (3 + 3), and one patient (0.7%) of PCa Gleason 7 (3 + 4). In group B, 6 patients (8.0%) received a diagnosis of BPH, 2 patients (2.7%) of PCa Gleason 6 (3 + 3), and one patient (1.3%) of PCa Gleason 7 (3 + 4) (Fig. 3). The Gleason score did not differ significantly between the two treatment groups.

The relative risk (RR) of having a diagnosis of PCa was 1.07 (95% CI [0.64-1.79]) and 0.89 (95% CI [0.41-1.95]) in group A and B, respectively (p = 0.95).

In the multivariate Cox regression analysis, treatment with Ly and Se (hazard ratio [HR] 1.38 [95% CI: 0.32-5.90]; p = 0.67) was not associated with an increased incidence of PCa.

Of all patients with PCa, 7 (77.8%) underwent radical prostatectomy, 1 (11.1%) underwent radiotherapy and 1 (11.1%) was in active surveillance.

There were no significant differences in terms of TEAEs between groups (p = 0.67). During the entire study, there was no evidence of significant changes with regard to laboratory parameters or vital signs.

**Discussion**

In recent years several data has been emerging about the putative role of chemoprevention and prostate cancer (Etminan et al., 2005; Lin et al., 2014).

In particular, Se, catechins from green tea and some derivatives of polyphenols have been demonstrated to be able to exhibit these preventive properties (Cimino et al., 2012). These characteristics are mostly to be referred to anti-oxidant activities and to the down-regulation of some proteins promoting cell proliferation or the inhibition of some chemokine.

However, the majority of these studies suffered from major limitations which consisted on the lack of assessment of blood concentrations of these supplements and also in the lack of a proper evaluation of the study population.

In according to such evidences, recent studies have questioned the role of selenium as a chemopreventive agent of prostate cancer(Gerstenberger et al., 2015; Kristal et al., 2014).

The SELECT study, the largest study of cancer prevention showed no preventive effect on PCa after 7 years of follow -up (Nicastro and Dunn, 2013).

A recent study of Gontero et al. also showed that the administration of high doses of Ly, catechins and Se in patients with high grade PIN (HGPIN) and/or ASAP was associated with a greater incidence of PCa at re- biopsy and increased expression of microRNAs involved in the progression PCa.

In this study we demonstrated that therapy with supplemental selenium (50 µg/die) and lycopene (5 mg) was not associated with a higher incidence of prostate cancer or of high-grade cancer. How can we then interpret these differences in results?

It is necessary to point out that the chemopreventive effects of selenium significantly differ in relation to serum levels at baseline.

In fact, several articles in the literature have shown that a low selenium status increased the risk of PCa in the absence of supplementary therapy (Etminan et al., 2005; Hurst et al., 2012).

Two small US studies have shown a reduced risk of 60% when the concentration of Se was higher than 0.69 µg/g and 40% when the concentration of Se was greater than 0.76 µg/g (Helzlsouer et al., 2000; Yoshizawa et al., 1998).

Kristal et al. however have shown that there is no benefit from the therapy in patients with low Se levels at baseline. However, in patients with high levels of Se (≥60 th percentile), supplementary therapy with and without vitamin E increases the risk of high-grade PCa by 91% (P = 0.007) (Kristal et al., 2014). These results suggest that supplementation with Se in patients with high baseline levels can become harmful.

In this context, there are some differences between our study and the SELECT trial, since herein we used 50 mcg/day of Se while in the latter a dose of 200 mcg/day have been used. On the contrary, our dosage was similar to the study of Gontero et al. (55 mcg/day) (Gontero et al., 2015), but we obtained different results. In fact, the study of Gontero et al. has shown that therapy with Ly supplementation led to an up-regulation of certain miRNAs able to exert oncogenic roles, such as MiR-23~27~24-2, but at the same time resulted in a

higher expression of some onco-miRNAs such as miR-199a, miR -92a, miR-30e, miR-16 with characteristics of promoting tumor proliferation (Gontero et al., 2015). Nevertheless, authors did not determine evaluation of Se serum concentration but only Ly.

Considering Ly levels, its serum concentrations have been differently evaluated in the Health Professionals Follow-up Study and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Study (Kirsh et al., 2006). In particular, Peters et al. indicated an increased risk of aggressive PCa with beta-carotene, whereas with lycopene no benefit, while according to Wu et al, lycopene was shown to be beneficial against PCa risk restricted to older participants and those without a family history of prostate cancer (Peters et al., 2007; Wu et al., 2004).

However, we may justify such discrepancies through different motivations. Firstly, our cohort of patients did not present at baseline high grade prostate intraepithelial neoplasia (PIN) and/or atypical small acinar proliferation (ASAP). We may in fact suppose that chemo supplementation with Se and Ly become harmful in patients with histological alteration at baseline, while in apparently healthy patients may not be able to determine a progression toward PCa. Secondly, cohort from Gontero et al. study was characterize by greater PSA levels at baseline respect to our cohort, strengthening the hypothesis of the apparent healthy situation of our setting (Gontero et al., 2015). Moreover, it is not elucidated why a dosage of 35 mg of Ly has been used in that study, a concentration that may have contributed to the increased risk incidence of PCa.

It is also important to point out, that we have previously demonstrated greater efficacy of combination therapy SeR 320 mg, Ly and Se + Tamsulosin 0.4 mg versus individual monotherapies with SeR 320 mg, Ly and Se or tamsulosin 0.4 mg in patients with moderate to severe LUTS secondary to clinical BPH after 1 year of follow-up. In addition to these results, this therapy is not able to determine an increase in the risk of PCa after 2

years of follow-up and with a dosage of selenium equal to 50 mcg/day and Ly equal to 5 mg/day.

Certainly our study is not depicted from the limitations. The lack of a measurement of the serum levels of selenium or other micronutrients has limited the interpretation of the role of such levels in the risk of PCa. In addition, the low rate of prostate cancer diagnosed may have limited the statistical evaluation of the study.

However, the strength of this work was to demonstrate the absence of an increased risk of PCa in patients receiving therapy with supplemental of Se and Ly for the presence of LUTS/BPH.

These results should be used with caution, however, in those categories of patients with LUTS/BPH as well as histological changes of high-grade PIN and/or ASAP for the possible increased risk of PCa.

**Conclusion**

Supplementary therapy with Selenium and Lycopene does not increase the risk of prostate cancer in patients with LUTS secondary to BPH after 2 years of follow -up.

**Ethical issues and consent to partecipate**

All participants provided written informed consent before enrolment and the study was conducted in accordance with regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996). The study was approved by our Institutional Research Ethics Committee (Policlinico Hospital). The study has been registered at ISRCTN register (ISRCTN78639965).

## Available data and materials

All available data are reported in the manuscript.

## Funding

None

## Author contribution

Morgia designed the study. Voce, Palmieri, Gentile, Iapicca, Giannantoni, Vespasiani, Carini, Arnone, Blefari, Santelli, Pareo and Russo collected data. Morgia and Russo performed statistical analysis and draft the manuscript.

## Aknowledgment

None

## Conflict of interest

Each author declares no conflict of interest.

## References

Bettuzzi, S., Brausi, M., Rizzi, F., Castagnetti, G., Peracchia, G., Corti, A., 2006. 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 research 66, 1234-1240.

Breslow, N., Chan, C.W., Dhom, G., Drury, R.A., Franks, L.M., Gellei, B., Lee, Y.S., Lundberg, S., Sparke, B., Sternby, N.H., Tulinius, H., 1977. Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. International journal of cancer. Journal international du cancer 20, 680-688.

Cantiello, F., Russo, G.I., Cicione, A., Ferro, M., Cimino, S., Favilla, V., Perdona, S., De Cobelli, O., Magno, C., Morgia, G., Damiano, R., 2016. PHI and PCA3 improve the prognostic performance of PRIAS and Epstein criteria in predicting insignificant prostate cancer in men eligible for active surveillance. World J Urol 34, 485-493.

Cimino, S., Sortino, G., Favilla, V., Castelli, T., Madonia, M., Sansalone, S., Russo, G.I., Morgia, G., 2012. Polyphenols: key issues involved in chemoprevention of prostate cancer. Oxid Med Cell Longev 2012, 632959.

Etminan, M., FitzGerald, J.M., Gleave, M., Chambers, K., 2005. Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis. Cancer Causes Control 16, 1125-1131.

Gasmi, J., Thomas Sanderson, J., 2013. Jacaric acid and its octadecatrienoic acid geoisomers induce apoptosis selectively in cancerous human prostate cells: a mechanistic and 3-D structure-activity study. Phytomedicine 20, 734-742.

Gerstenberger, J.P., Bauer, S.R., Van Blarigan, E.L., Sosa, E., Song, X., Witte, J.S., Carroll, P.R., Chan, J.M., 2015. Selenoprotein and antioxidant genes and the risk of high-grade prostate cancer and prostate cancer recurrence. Prostate 75, 60-69.

Gontero, P., Marra, G., Soria, F., Oderda, M., Zitella, A., Baratta, F., Chiorino, G., Gregnanin, I., Daniele, L., Cattel, L., Frea, B., Brusa, P., 2015. A randomized double-blind placebo controlled phase I-II study on clinical and molecular effects of dietary supplements in men with precancerous prostatic lesions. Chemoprevention or "chemopromotion"? Prostate 75, 1177-1186.

Helzlsouer, K.J., Huang, H.Y., Alberg, A.J., Hoffman, S., Burke, A., Norkus, E.P., Morris, J.S., Comstock, G.W., 2000. Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer. J Natl Cancer Inst 92, 2018-2023.

Hurst, R., Hooper, L., Norat, T., Lau, R., Aune, D., Greenwood, D.C., Vieira, R., Collings, R., Harvey, L.J., Sterne, J.A., Beynon, R., Savovic, J., Fairweather-Tait, S.J., 2012. Selenium and prostate cancer: systematic review and meta-analysis. Am J Clin Nutr 96, 111-122.

Joniau, S., Goeman, L., Roskams, T., Lerut, E., Oyen, R., Van Poppel, H., 2007. Effect of nutritional supplement challenge in patients with isolated high-grade prostatic intraepithelial neoplasia. Urology 69, 1102-1106.

Kenfield, S.A., Van Blarigan, E.L., DuPre, N., Stampfer, M.J., E, L.G., Chan, J.M., 2015. Selenium supplementation and prostate cancer mortality. Journal of the National Cancer Institute 107, 360.

Kheirandish, P., Chinegwundoh, F., 2011. Ethnic differences in prostate cancer. British journal of cancer 105, 481-485.

Kirsh, V.A., Hayes, R.B., Mayne, S.T., Chatterjee, N., Subar, A.F., Dixon, L.B., Albanes, D., Andriole, G.L., Urban, D.A., Peters, U., Trial, P., 2006. Supplemental and dietary

vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. J Natl Cancer Inst 98, 245-254.
Klein, E.A., Thompson, I.M., 2012. Chemoprevention of prostate cancer: an updated view. World journal of urology 30, 189-194.
Kristal, A.R., Darke, A.K., Morris, J.S., Tangen, C.M., Goodman, P.J., Thompson, I.M., Meyskens, F.L., Jr., Goodman, G.E., Minasian, L.M., Parnes, H.L., Lippman, S.M., Klein, E.A., 2014. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. J Natl Cancer Inst 106, djt456.
Lin, Y.W., Hu, Z.H., Wang, X., Mao, Q.Q., Qin, J., Zheng, X.Y., Xie, L.P., 2014. Tea consumption and prostate cancer: an updated meta-analysis. World J Surg Oncol 12, 38.
Michaelsen, F.W., Saeed, M.E., Schwarzkopf, J., Efferth, T., 2015. Activity of Artemisia annua and artemisinin derivatives, in prostate carcinoma. Phytomedicine 22, 1223-1231.
Mohanty, N.K., Saxena, S., Singh, U.P., Goyal, N.K., Arora, R.P., 2005. Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. Urologic oncology 23, 383-385.
Morgia, G., Russo, G.I., Voce, S., Palmieri, F., Gentile, M., Giannantoni, A., Blefari, F., Carini, M., Minervini, A., Ginepri, A., Salvia, G., Vespasiani, G., Santelli, G., Cimino, S., Allegro, R., Collura, Z., Fragala, E., Arnone, S., Pareo, R.M., 2014. Serenoa repens, lycopene and selenium versus tamsulosin for the treatment of LUTS/BPH. An Italian multicenter double-blinded randomized study between single or combination therapy (PROCOMB trial). Prostate 74, 1471-1480.
Nicastro, H.L., Dunn, B.K., 2013. Selenium and prostate cancer prevention: insights from the selenium and vitamin E cancer prevention trial (SELECT). Nutrients 5, 1122-1148.
Peters, U., Leitzmann, M.F., Chatterjee, N., Wang, Y., Albanes, D., Gelmann, E.P., Friesen, M.D., Riboli, E., Hayes, R.B., 2007. Serum lycopene, other carotenoids, and prostate cancer risk: a nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 16, 962-968.
Ramamoorthy, V., Rubens, M., Saxena, A., Shehadeh, N., 2015. Selenium and vitamin E for prostate cancer--justifications for the SELECT study. Asian Pacific journal of cancer prevention : APJCP 16, 2619-2627.
Sebastiano, C., Vincenzo, F., Tommaso, C., Giuseppe, S., Marco, R., Ivana, C., Giorgio, R., Massimo, M., Giuseppe, M., 2012. Dietary patterns and prostatic diseases. Front Biosci (Elite Ed) 4, 195-204.
Tsai, C.H., Tzeng, S.F., Hsieh, S.C., Lin, C.Y., Tsai, C.J., Chen, Y.R., Yang, Y.C., Chou, Y.W., Lee, M.T., Hsiao, P.W., 2015. Development of a standardized and effect-optimized herbal extract of Wedelia chinensis for prostate cancer. Phytomedicine 22, 406-414.
Van Poppel, H., Tombal, B., 2011. Chemoprevention of prostate cancer with nutrients and supplements. Cancer management and research 3, 91-100.
Vinceti, M., Dennert, G., Crespi, C.M., Zwahlen, M., Brinkman, M., Zeegers, M.P., Horneber, M., D'Amico, R., Del Giovane, C., 2014. Selenium for preventing cancer. The Cochrane database of systematic reviews 3, CD005195.
Wu, K., Erdman, J.W., Jr., Schwartz, S.J., Platz, E.A., Leitzmann, M., Clinton, S.K., DeGroff, V., Willett, W.C., Giovannucci, E., 2004. Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 13, 260-269.
Yoshizawa, K., Willett, W.C., Morris, S.J., Stampfer, M.J., Spiegelman, D., Rimm, E.B., Giovannucci, E., 1998. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. Journal of the National Cancer Institute 90, 1219-1224.

## Figure legends

**Fig. 1.** Disposition of subjects. Subject Consolidated Standards of Reporting Trials (CONSORT) diagram

**Fig. 2.** Mean PSA during follow-up in Group A and B. Bars indicated standard deviation.

**Fig. 3.** Restricted crude rates of prostate cancer are shown. The P value is for the comparison of SeR+Se+Ly with control, with the use of the Mantel–Cox test.



**Figure 1**

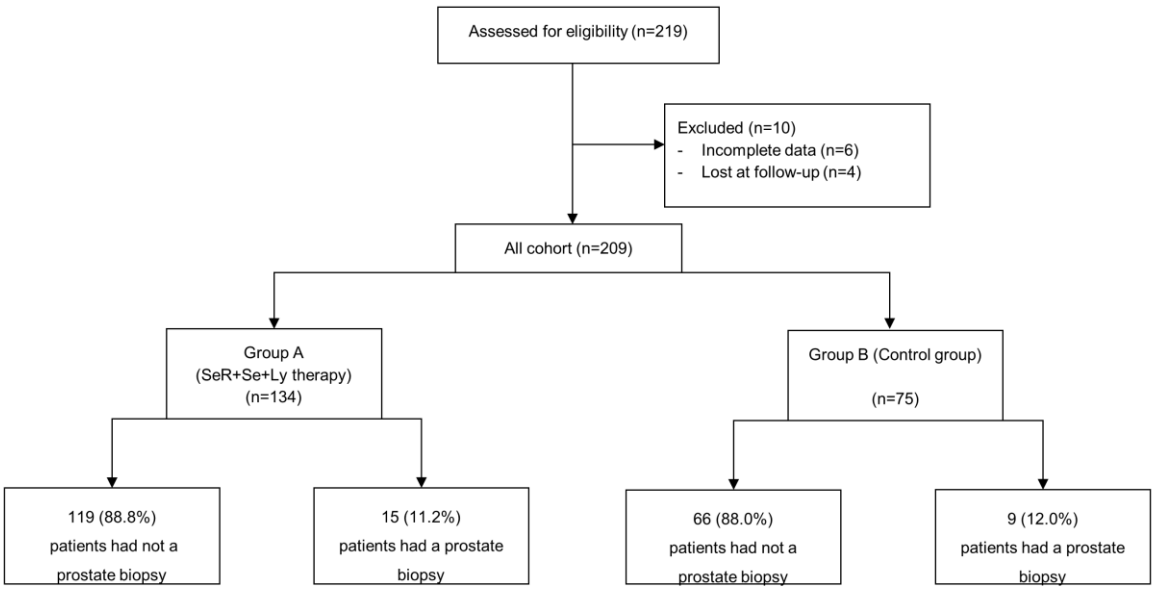


**Figure 2**

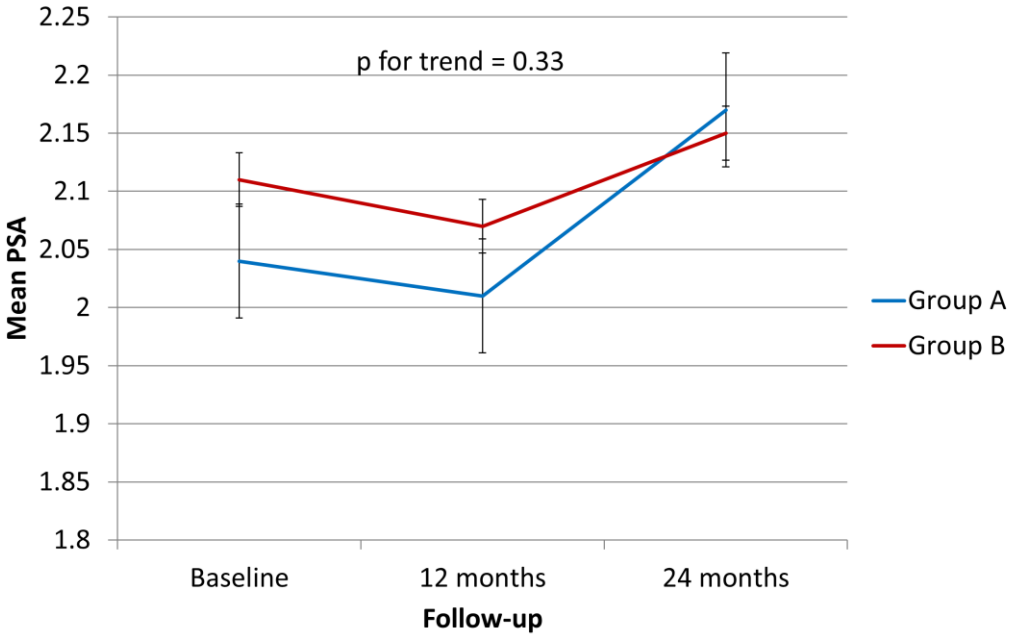
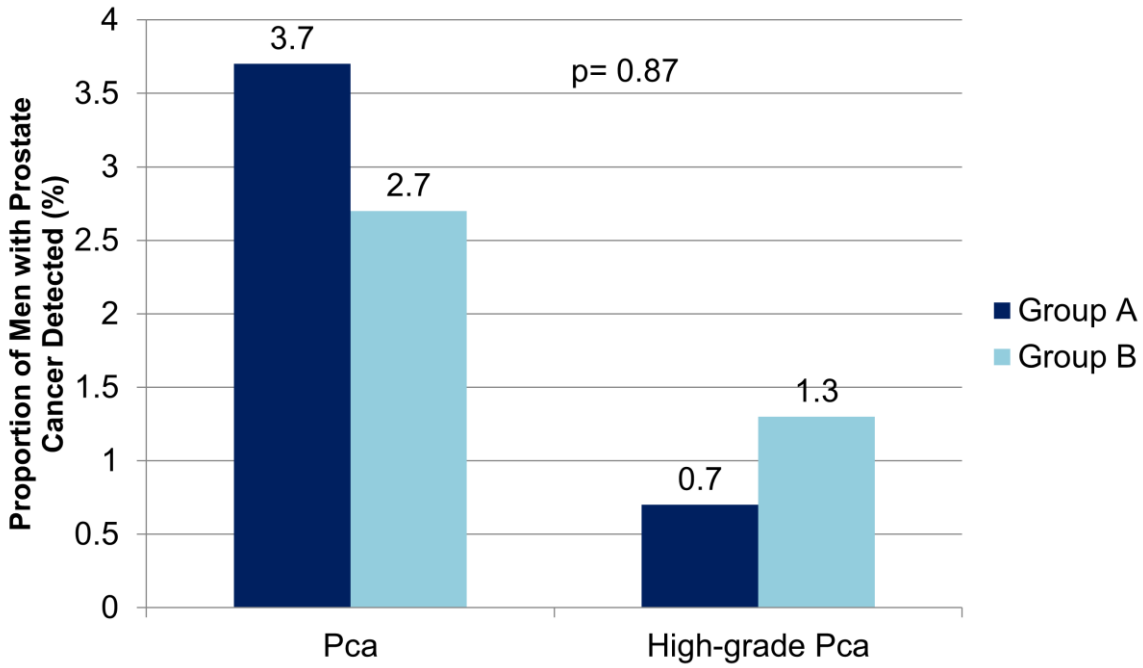


**Figure 3**




Graphical abstract

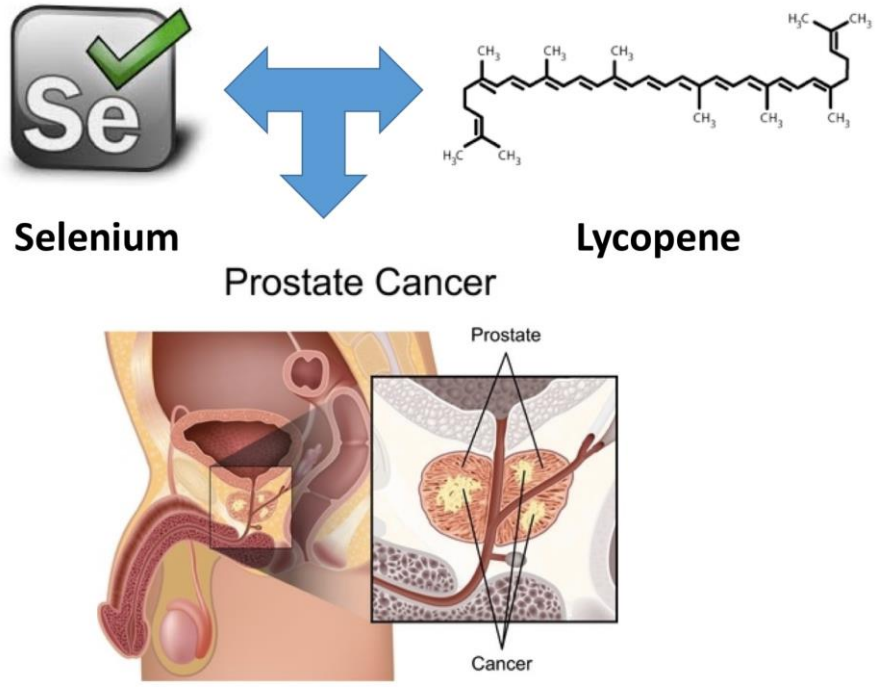


Table 1

| **Baseline characteristics of patients.** | | | |
|---|---|---|---|
| | **Group A (n = 134)** | **Group B (n = 75)** | **p-value*** |
| Age, median (IQR) | 65.0 (60.0-69.0) | 66.0 (60.75-71.0) | 0.09 |
| BMI, median (IQR) | 27.4 (24.0-29.4) | 27.0 (24.5-29.5) | 0.37 |
| PSA (ng/ml), median (IQR) | 2.04 (1.29-3.25) | 2.11 (1.23-3.10) | 0.42 |
| PSA ratio (%), median (IQR) | 21.0 (17.4-24.3) | 20.5 (17.2-24.1) | 0.31 |
| PSA density, median (IQR) | 0.17 (0.11-0.22) | 0.16 (0.10-0.23) | 0.52 |
| Prostate Volume (cc), median (IQR) | 44.0 (35.0-52.0) | 45.0 (38.0-53.25) | 0.12 |
| Peak-flow (ml/s), median (IQR) | 11.2 (1.0-13.3) | 11.8 (9.0-13.0) | 0.28 |
| Post-void volume (ml), median (IQR) | 50.0 (27.5-75.0) | 50.0 (30.0-80.0) | 0.60 |
| IPSS, median (IQR) | 19.0 (17.5-22.0) | 19.0 (18.0-22.25) | 0.14 |
| Family history of prostate cancer, no. (%) | 19 (14.2) | 10 (13.3 | 0.34 |
| Cores at prostate biopsy, median (IQR) | 14 (12-17) | 13 (12-18) | 0.61 |
| BMI = body mass index; PSA = prostate specific antigen; IPSS = international prostate symptoms score; IQR = interquartile range<br>*Mann-Whitney test U test | | | |

Table 1