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Original Article

Association between selenium and lycopene supplementation and incidence of prostate cancer: Results from the post-hoc analysis of the procomb trial

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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.

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

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

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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 320 mg of supercritical CO2 lipidic extract SeR containing 85% of fatty acids sterols, selenium (50mcg) and lycopene (5 mg) (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