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Randomized control trials

Tomato-based randomized controlled trial in prostate cancer patients: Effect on PSA

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SUMMARY

Background & aims: The effect of lycopene-containing foods in prostate cancer development remains undetermined. We tested whether a lycopene-rich tomato intervention could reduce the levels of prostate specific antigen (PSA) in prostate cancer patients.

Methods: Prior to their curative treatment, 79 patients with prostate cancer were randomized to a nutritional intervention with either 1) tomato products containing 30 mg lycopene per day; 2) tomato products plus selenium, omega-3 fatty acids, soy isoflavones, grape/pomegranate juice, and green/black tea (tomato-plus); or 3) control diet for 3 weeks.

Results: The main analysis, which included patients in all risk categories, did not reveal differences in changes of PSA-values between the intervention and control groups. Post-hoc, exploratory analyses within intermediate risk ($n = 41$) patients based on tumor classification and Gleason score post-surgery, revealed that median PSA decreased significantly in the tomato group as compared to controls (−2.9% and +6.5% respectively, $p = 0.016$). In separate post-hoc analyses, we observed that median PSA-values decreased by 1% in patients with the highest increases in plasma lycopene, selenium and C20:5 n-3 fatty acid, compared to an 8.5% increase in the patients with the lowest increase in lycopene, selenium and C20:5 n-3 fatty acid ($p = 0.003$). Also, PSA decreased in patients with the highest increase in lycopene alone ($p = 0.009$).

Conclusions: Three week nutritional interventions with tomato-products alone or in combination with selenium and n-3 fatty acids lower PSA in patients with non-metastatic prostate cancer. Our observation suggests that the effect may depend on both aggressiveness of the disease and the blood levels of lycopene, selenium and omega-3 fatty acids.

Abbreviations: C20:5 n-3, Eicosapentaenoic acid; FAME, Fatty acid methyl ester; FFQ, Food Frequency Questionnaire; HPLC, High Performance Liquid Chromatography; ICP-MS, Inductively Coupled Plasma Mass Spectrometry; PUFA, poly-unsaturated fatty acids; PSA, prostate specific antigen; RCT, randomized controlled trial; SHBG, sex hormone-binding globulin; SNP, Single Nucleotide Polymorphism; WCRF, World Cancer Research Fund.

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1. Introduction

Prostate cancer is the second most common cancer in men in the world with nearly 900 000 new cases diagnosed each year [1]. The incidence and mortality of prostate cancer show large geographical differences [2]. The epidemiological patterns suggest that lifestyle and dietary factors impact the occurrence of prostate cancer. Tomatoes have been identified as one possible candidate for reducing the risk of prostate cancer with lycopene as the major potential active component [3]. While the Second Expert Report by the World Cancer Research Fund (WCRF) [4] concluded that lycopene containing foods (mainly tomatoes) probably protect against prostate cancer, the recently released Continuous Update Project Report from WCRF states that no conclusion was possible due to limited evidence [5].

Prostate specific antigen (PSA) is an important biomarker used in clinical risk assessments, follow-ups and as part of risk stratification of prostate cancers patients [6,7]. The effect of tomatoes or lycopene-containing foods on PSA values in patients with established prostate cancer has not been well documented. In an uncontrolled trial, a tomato sauce intervention for 3 weeks reduced PSA in a subgroup of prostate cancer patients [8], while lycopene supplements or extracts seemed to be less effective in reducing PSA [9–11]. However, the lycopene contents of tomato-based foods, as well as lycopene bioavailability varies considerably [12] and may impact the efficacy of tomato-based interventions.

Several other foods or food components have also been suggested to protect against prostate cancers [5]. The WCRF concludes that there is still limited evidence for the association between prostate cancer and these dietary components. Thus a second intervention arm with selenium, omega-3 fatty acids, soy isoflavones, grapes, pomegranates, tea and tomato-products was included in our study to investigate possible additive effects on PSA.

The present 3-arm randomized controlled trial (RCT), aimed to test whether a tomato based lycopene-rich diet changed the kinetics of PSA in patients with non-metastatic prostate cancer during the three weeks period preceding the patients' curative treatment. Furthermore, we performed two sets of exploratory post-hoc analyses. First, we hypothesized that a lycopene-rich diet during this period leads to a more favorable PSA profile in intermediate risk patients as compared to a matched control group. Secondly, we tested whether the effects on PSA depend on bioavailability of the active treatment components.

2. Subjects and methods

2.1. Ethics statement

This study was approved by the regional ethics committee in Norway (REK Sør, no. S-06187). The study is registered in ClinicalTrials.gov with no. NCT00433797. All participants signed a letter of informed consent.

2.2. Subjects and study design

Subjects for this parallel group RCT were recruited from two clinical centers within the Oslo University Hospital, Oslo, Norway; the Norwegian Radium Hospital and Aker University Hospital between June of 2007 and March of 2012. Patients diagnosed with non-metastatic prostate cancer (N0 and M0 as confirmed by negative chest X-ray, bone scintigraphy and pelvic MRI or CT), and scheduled for either radical prostatectomy or high-dose radiotherapy consisting of a combination of high-dose rate brachytherapy and pelvic external beam radiotherapy [13] were considered eligible. Patients were invited to participate in the study by their counseling urologists, oncologist or study nurses. Exclusion criteria: White blood cells outside normal reference window; Hb < 11 g/dL; prior endocrine treatment; <5 year life-expectancy; ECOG score >1; incontinence/urinary retention; critical comorbidity (e.g. cardiovascular disease, chronic obstructive pulmonary disease, insulin dependent diabetes mellitus, vasculitis, inflammatory bowel syndrome or other conditions which could influence radiation therapy).

The risk classification of the prostate cancer patients includes PSA, pT-staging and Gleason score. Patients with low or intermediate risk according the D'Amico risk classification [14] were considered eligible for the study. In addition, 13 patients with Gleason score 8 and 9, pT3a-stage or PSA ≥20 μg/L (provided that they fulfilled all other inclusion and exclusion criteria) were also considered eligible after individual evaluation by their oncologist/urologist.

After surgery, the prostatectomy specimens enable new and more precise tumor description [15]. Taking into account this post-surgery information, we defined an adjusted/alternative risk classification for prostatectomized patients in part following the 2013 European guidelines [16]. This adjusted risk classification was based on pT category and the Gleason score in the prostatectomy specimen and included the pre-intervention PSA. Three risk groups emerged among the study group: Low risk (pT1c-pT2a, and PSA < 10 μg/L, and, Gleason score ≤ 6); Intermediate risk (pT2b-pT2c, and/or 10 μg/L ≤ PSA <20 μg/L, and/or Gleason score 7); or High risk (pT3, and/or ≥ PSA 20 μg/L, and/or Gleason score 8–10).

2.3. Randomization and blinding

At inclusion, patients were randomized to one of three arms; a control group, a tomato group, and a tomato-plus group. Randomization was computer generated real-time by the "Department of Clinical Research Support" at the Oslo University Hospital at time of inclusion. By assigning single digit numbers to the interventions, randomization was blinded for the investigators until after initial statistical analyses were performed.

2.4. Blood samples and handling

All blood samples were collected at the hospitals during routine clinical visits. Blood samples were drawn by venipuncture before the start of the diet-intervention, and at the end of the diet-intervention (i.e. shortly before surgery/radiotherapy). For plasma samples, blood samples (standard heparin, EDTA and citrate tubes) were centrifuged (1500*g* for 10 min) at 4 °C. Red blood cells were collected from centrifuged citrate blood samples after the collection of citrate plasma and removal of the buffy coat. All samples were stored at −70 °C until analysis.

2.5. Interventions

The tomato intervention included tomato products with a content of 30 mg lycopene per day (see Supplementary Table 1 for details). In addition to the same amount of tomato products, the tomato-plus intervention also included green tea (a cup made from 1 sachet) and black tea (a cup made from 1 sachet), pomegranate- and grape juice (330 mL of each), 200 mg soy isoflavones, 200 μg 1-selenomethionin and 3.13 g n-3 fatty acids per day (for details and producers see Supplementary Table 2). The patients in the control group were encouraged to continue their habitual diet.

In order to select tomato products to be included in the study, we measured lycopene contents (experimental procedure below) in 170 tomato products commercially available in Norway (Supplementary Table 3). This screening revealed large differences

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