ELSEVIER

Urologic Oncology: Seminars and Original Investigations 23 (2005) 383–385

UROLOGIC ONCOLOGY

Original article

Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia

Nayan Kumar Mohanty, M.S., M.Ch.(URO)*, Sunita Saxena, M.D.(PATH), Uday Pratap Singh, M.S., Neeraj K. Goyal, M.S., Rajender Prakash Arora, M.S.

Department of Urology, V.M. Medical College & Safdarjang Hospital, New Delhi, India

Received 5 May 2004; received in revised form 9 May 2005; accepted 10 May 2005

Abstract

Objective: Because of its long latency, slow growing nature, and high prevalence, prostate cancer is the best model for chemoprevention. High-grade prostate intraepithelial neoplasia (HGPIN) is a precursor of prostate cancer. Chemoprevention with lycopene has shown definite results in prostate cancer. We undertook a study to use lycopene as a chemopreventive agent in the treatment of HGPIN for preventing prostate cancer from developing in this vulnerable group of patients.

Materials and Methods: A total of 40 patients with HGPIN were randomized into 2 groups: one received 4 mg lycopene twice a day for one year, and the other was periodically followed up. Total follow-up was one year.

Results: Our results show that lycopene can delay or prevent HGPIN from developing into occult prostate cancer, and there exists an inverse relationship between lycopene and prostate-specific antigen. Being a vegetable carotenoid, lycopene is a safe drug to be used for a longer period without any adverse reaction.

Conclusion: Lycopene is an effective chemopreventive agent in the treatment of HGPIN, with no toxicity and good patient tolerance.

Keywords: Lycopene; High grade prostate intraepithelial neoplasia; Prostate cancer

1. Introduction

Coined in the mid 1970s by Dr. Michael B. Sporn, the term chemoprevention is defined as the pharmacologic intervention with a natural or synthetic compound to reverse or suppress carcinogenesis in its early or premalignant stages so as to prevent the development of invasive cancer [1]. Recent advances in epidemiology and a better understanding of molecular biology supported by clinical research have prompted chemoprevention to the forefront of this new approach for cancer control. The complex process of carcinogenesis can evolve over decades, from the first mutagenic initiation through multiple stages before finally ending in invasive cancer. During this process, a number of molecular and cellular alterations affected by several exogenous and endogenous factors either enhance or retard the process of carcinogenesis. Sporn's proposal of reversing this process by pharmacologic agents gave birth to the concept of chemoprevention. The concept of primary chemoprevention for prostate cancer gained momentum in the 1990s because of the disease high prevalence, slowly progressive nature, and long latency [2–4]. The ideal therapeutic intervention would arrest disease progression during the latency period and decrease the incidence of clinical disease. The success of chemoprevention depends on several factors:

- Treatment given to an otherwise healthy but a high-risk individual in whom prostate cancer develops.
- Those therapeutic agents given must offer low-to-no toxicity with a simple dose regime for better patient tolerance.
- The efficacy of these agents should be beyond doubt.
- Motivate patients to use these agents all their lives [5].

Because research has shown that diet plays a great role in the development of prostate cancer, many researchers have suggested that fat, soya, green tea, lycopene, selenium, vitamins, and retinoids are among others as modifiers of

* Corresponding author. Tel.: +91-11-24676704; fax: +91-11-26190954.

E-mail address: nayankm@yahoo.co.in (N.K. Mohanty).

1078-1439/05/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.urolonc.2005.05.012

prostate cancer risk. Data suggest that 13% of prostate cancer cases may be preventable by reducing saturated fat intake [6]. Lycopene, a red carotenoid pigment, is found abundantly in various fruits like guava, pink grapefruit, watermelon, and tomato. With its potent antioxidant activity, lycopene may protect cellular components from reactive oxygen radical species. Epidemiologic data show that lycopene consumption is associated with a decreased risk as well as a possible reduction in prostate cancer growth [7].

High-grade prostate intraepithelial neoplasia (HGPIN) is now identified as a premalignant condition of prostate malignancy that is a well-established histological entity. Many benign prostatic adenomas that are surgically removed will show HGPIN in their histology. HGPIN has been graded as low (grade I) and high (grades II and III) histologically. If identified early and kept on chemoprevention, these patients with HGPIN can be prevented from the development of occult prostate cancer in the future because it is the potential precursor of ovoid prostate cancer. We undertook this study to treat HGPIN with lycopene and follow-up for 2 years with a control group in a randomized fashion to establish the efficacy and safety of lycopene as a chemopreventive agent in HGPIN.

2. Materials and methods

A total of 230 patients undergoing transurethral resection of the prostate for benign prostatic hyperplasia (BPH) was reviewed for our study. After a thorough clinical examination, all patients underwent uroflowmetry, digital rectal examination (DRE), total serum prostate-specific antigen (PSA), serum lycopene, transrectal ultrasonography, and prostate biopsy only in suspected patients. Of the 230 patients, serum PSA was increased in 38 (>4 ng/ml), and another 30 had an abnormal DRE. All 68 patients were subjected to sextant prostate biopsy, of which 15 (11 with an abnormal DRE and 4 with increased PSA) had malignancy and were subsequently excluded from the study, leaving a total of 215 patients for evaluation in our study.

After being established as BPH clinically, all 215 patients underwent transurethral resection of the prostate as a standard treatment for their features of prostatism. Tissue was sent for histopathologic examination conducted by one onco-pathologist for uniformity. Of the 215 patients, 160 had benign hyperplasia of prostate, 11 had low-grade prostate intraepithelial neoplasia (grade I) along with BPH, 40 had HGPIN (grade II in 16 and grade III in 24 patients), and another 4 had occult prostate malignancy along with HGPIN in their histopathology report, respectively (Table 1).

There were 40 patients with HGPIN who were randomized into 2 groups: group A (n = 20) and group B (n = 20). The patients in group A (ie, study group) had HGPIN, with grade II disease in 8 and HGPIN in 12, while the same number was included in the control group, group B for uniformity. All 20 patients in group A (study group) received 4 mg lycopene (Lyc-O-Mato, LycoRed Natural Products Industries, Ltd., Beer-Sheva, Israel) twice a day for one year continuously and were followed for another year. None of the 20 patients in group B (control group) received any medication and were only followed for 2 years periodically.

Table 1
Serum PSA and serum lycopene

	Mean PSA (ng/ml)	Mean serum lycopene (ng/ml)
Study group A (20 patients)		
Before therapy	6.07	360
After therapy	3.5	680
Control group B (20 patients)		
Before therapy	6.55	378
After therapy	8.06	180

The baseline serum lycopene, total PSA of both groups was obtained before therapy. Both groups were followed for 2 years at 3 monthly intervals with serum lycopene and serum PSA, and DRE. Prostate biopsy was performed as and when indicated during follow-up. Normal serum PSA level in our laboratory was 0–4 ng/dL (during our study), and the serum lycopene level was 300 ng/dL. Both groups were advised to continue their normal diet, but the control group was advised to reduce its intake of tomato and melon.

3. Results

The serum PSA level in the treated group A decreased for a mean level of 6.07–3.5 ng/ml, while in the control group B, it increased from a mean value of 6.55 to 8.06 ng/ml. Similarly, the serum lycopene level was increased from the mean value of 360 to 680 ng/ml in group A but decreased from a mean value of 378 to 180 ng/ml in the group B. During follow-up, 6 patients had increased PSA in group A and 9 in group B. Subsequent prostate biopsy in these patients with increased PSA showed 4 patients with BPH and 2 with adenocarcinoma in study group A, while the totals were 3 with BPH and 6 with adenocarcinoma in the control group B.

On follow-up DRE in patients in group A, suspicious nodules were felt in 2 (10%) who also had increased PSA, on whom biopsy was proved adenocarcinoma prostate. In patients in group B, follow-up DRE showed suspicious nodule in 6 (30%) with increased PSA and subsequent biopsy proved adenocarcinoma. No adverse effects were observed in the lycopene therapy group. Our study clearly indicates:

- HGPIN is a precursor of ovoid prostate malignancy.
- Lycopene can act as a chemopreventive agent in preventing or delaying the development of malignancy in these high-risk patients.
- There exists an inverse relationship between serum PSA and serum lycopene level.

- Being a vegetable carotenoid, lycopene is very safe for prolonged use.

4. Discussion

Prostate cancer is an excellent model for chemoprevention therapy because of its high prevalence, slowly progressive malignancy, and long latency. There is an abundance of literature available indicating that lycopene reduces the occurrence or progression of prostate cancer [8,9], inverse association between plasma lycopene, and other carotenoids and prostate cancer [10].

In their trial with 47,894 health professional for 6 years, Giovannucci et al. [11] have shown that lycopene reduces the risk of prostate malignancy by 24% to 36%. Other research work supports this fact that lycopene reduces occurrence or progression of prostate cancer. A cohort study including approximately 14,000 Adventist men who consumed tomato products during a 6-year period found that there was an association with lower prostate cancer risk [6]. This finding was substantiated in a prospective cohort study from health professionals in which lycopene intake from tomato-based foods was inversely associated with [12]. These investigations reported that men ingesting 2 or more servings of tomato sauce per week had a 36% reduction in prostate cancer risk, compared to their counterpart, who did not consume tomato sauce.

In their trial, Kucuk et al. [13] have shown that lycopene results in less diffuse involvement of prostate gland with HGPIN as compared to the control group. Lycopene has many modes of action, of which its anti-proliferative insulin-like growth factor-1 inhibition, differentiation and apoptosis, connexin and gap junctional intercellular communication are identified as useful in the carcinogenesis inhibition process apart from its role as a powerful antioxidant. Our study showed that lycopene can very effectively be used as a chemopreventive agent in preventing or delaying HGPIN from becoming an ovoid prostate malignancy.

5. Conclusions

This initial small trial has shown that lycopene is an effective chemopreventive agent in preventing HGPIN from becoming prostate cancer. However, a larger clinical trial is warranted to establish the potentiality of lycopene as a chemopreventive agent for the treatment of prostate cancer.

References

[1] Khuri FR, Sabichi AL, Hong WK, et al. The chemoprevention of cancer. In: Pollock RE, editor. Manual of Clinical Oncology. New York: Wiley-Liss, Inc., 1999. p. 163–9.
[2] Szarka CE, Grana G, Engstrom PF. Chemo prevention of cancer. Curr Probl Cancer 1994;18:6–10.
[3] Lippman SM, Benner SE, Hong WK. Cancer chemo prevention. J Clin Oncol 1994;12:851–73.
[4] Kelloff GJ, Lieberman R, Steele VE, et al. Chemo prevention of prostate cancer: Concepts and strategies. Eur Urol 1999;35:342–8.
[5] Ekman P. Genetic and environmental factors in prostate cancer genesis: Identifying high risk cohorts. Eur Urol 1999;35:362–70.
[6] Henkin JH, Zhao LP, Wilkens LR, et al. Attributable risk of breast, prostate and lung cancer in Hawaii due to saturated fat. Cancer Causes Control 1992;3:17–22.
[7] Mills PK, Beeson WL, Philips RL, et al. Cohort study of diet, life style and prostate cancer in Adventist men. Cancer 1989;64:582–90.
[8] Gann PH, Ma J, Giovannucci E. Lycopene reduced occurrence or progression of cancer prostate. Cancer Res 1999;59:1225–30.
[9] Rao AV, Fleshner N, Agarwal S, et al. Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: A case-control study. Nutr Cancer 1999;33:159–64.
[10] Lu QY, Hung JC, Heber D, et al. Inverse association between plasma lycopene & other carotenoids & cancer Prostate. Cancer Epidemiol Biomarkers Prev 2001;10:749–56.
[11] Giovannucci E, Rimm EB, Liu Y, et al. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 2002;94:391–8.
[12] Giovannucci E, Ascherio A, Rimm EB, et al. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995;87:1767–77.
[13] Kucuk O, Sarkar FH, Sakr W, et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomarkers Prev 2001;8:861–8.