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Review

Role of lycopene and tomato products in prostate health

Maria Stacewicz-Sapuntzakis*, Phyllis E. Bowen

Department of Human Nutrition, University of Illinois at Chicago, 1919 West Taylor St. Chicago, IL 60612, USA

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Abstract

Epidemiological evidence associating the decreased risk of prostate cancer with frequent consumption of tomato products inspired us to conduct a small intervention trial among patients diagnosed with prostate adenocarcinoma. Tomato sauce pasta was consumed daily for 3 weeks before their scheduled prostatectomy, and biomarkers of tomato intake, prostate cancer progression and oxidative DNA damage were followed in blood and the available prostate tissue. The whole food intervention was so well accepted by the subjects that the blood lycopene (the primary carotenoid in tomatoes responsible for their red color) doubled and the prostate lycopene concentration tripled during this short period. Oxidative DNA damage in leukocytes and prostate tissues was significantly diminished, the latter mainly in the tumor cell nuclei, possibly due to the antioxidant properties of lycopene. Quite surprising was the decrease in blood prostate-specific antigen, which was explained by the increase in apoptotic death of prostate cells, especially in carcinoma regions. Prostate cancer cell cultures (LNCaP) were also sensitive to lycopene in growth medium, which caused an increased apoptosis and arrested the cell cycle. A possible explanation of these promising results may reside in lycopene effects on the genes governing the androgen stimulation of prostate growth, cytokines and on the enzymes producing reactive oxygen species, all of which were recently discovered by nutrigenomic techniques. Other phytochemicals in tomato may act in synergy with lycopene to potentiate protective effects and to help in the maintenance of prostate health.

Keywords: Carotenoid; Cancer; Oxidative stress; Apoptosis

The prostate, a major male accessory gland, is a potential source of serious disorders affecting health and the quality of life in older men. The walnut-size gland envelops the urethra just below the bladder, and several pathological conditions have a tendency to obstruct the flow of urine which may damage the bladder and kidneys. Prostate disorders include inflammation (prostatitis), benign prostatic hyperplasia (BPH) and prostate cancer. While acute or chronic prostatitis may afflict any adult male, by the age of 70 years, more than 40% of men develop an enlargement of prostate due to BPH, and by the age of 80 years, most will have prostate cancer. The treatment for cancer may involve radiation, various surgical procedures, anti-androgen hormonal therapy, with possible side effects of urinary incontinence and impotence. These perspectives cause many doctors and patients to accept a "watchful waiting" strategy, since cancers of the prostate are relatively slow growing, especially in older men.

Prostate cancer is a worldwide health problem, most common in northwestern Europe (Scandinavian countries) and North America, but rare in East Asia (China, Japan). An estimated 230,000 new cases will occur in the US in 2004, with 30,000 deaths in the same year, placing prostate cancer as the second leading cause of cancer death in US men [1]. Incidence rates are the highest in African American men and Caribbean men of African descent. Besides age, ethnic origin, and family history (genetic predisposition), the risk factors for prostate cancer include smoking, high intake of fat, obesity and lack of exercise [2]. Therefore the prevention of prostate diseases is one of the pressing health issues in the developed countries. An exploration of many lifestyle factors, including dietary compounds and their mechanism of action, is underway through epidemiological

* Corresponding author. Tel.: +1 312 996 1210; fax: +1 312 413 0319.
E-mail address: msapuntz@uic.edu (M. Stacewicz-Sapuntzakis).

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surveys, clinical trials and experiments with animals, cell and tissue cultures.

Epidemiological evidence of the protective role of tomatoes in diet emerged from careful evaluation of large U.S. cohort studies [3,4]. Men who consumed the most tomato products had significantly lower risk of developing prostate cancer. Therefore our research group at the University of Illinois embarked on a program of investigating prostate health issues related to dietary intake of tomatoes and their red pigment, a carotenoid named lycopene after the genus *Lycopersicon*. Tomatoes are the main source of lycopene in American diet and the presence of lycopene in serum can be considered a marker of tomato consumption. The bioavailability of lycopene is increased by cooking [5] and the presence of fat in the same meal, which favors the formation of carotenoid containing micelles and their absorption in the intestine [6]. In epidemiological studies the incidence of aggressive prostate cancer declined with increasing plasma lycopene concentration [7].

In order to investigate the feasibility of a whole food intervention and its efficacy, we conducted a pilot project [8], recruiting patients suspected of harboring prostate cancer, because of rising prostate specific antigen (PSA) levels in serum, or due to abnormality of prostate detected by digital examination. Thirty- two patients were diagnosed with adenocarcinoma of the prostate and agreed to consume tomato pasta every day during 3 weeks before their scheduled prostatectomy. The dishes were prepared by our staff and contained 30 mg lycopene from commercial spaghetti sauce. The patients reported good adherence to the diet, consuming on average 81.7% of the total dose, which amounted to 26.8 mg lycopene/day, compared with their usual mean intake of 5 mg/day. The assessment of their serum lycopene by high performance liquid chromatography (HPLC) confirmed the excellent compliance to tomato sauce regimen (Table 1), because the mean lycopene concentration doubled during this short intervention, from 638 nM to 1258 nM ($P<0.001$).

We have also measured the lycopene content of their prostate tissue, in biopsy performed at the time of cancer diagnosis before the intervention, and in the resected tissue obtained during the scheduled prostatectomy. The mean lycopene concentration tripled from 0.28 to 0.82 nmol/g ($P<0.001$).

Could this significant increase in serum and tissue lycopene concentrations have any effect on the oxidative stress of the subjects? We found indications of decreased oxidative damage to DNA, as evidenced by the ratio of 8-hydroxy-2′-deoxyguanosine(8OHdG) to 2′-deoxyguanosine (dG), measured by HPLC with electrochemical and UV detection after the extraction and hydrolysis of DNA from leukocyte nuclei. The 8OHdG/10^5dG ratio decreased from 0.61 to 0.48 ($P=0.005$) during the trial interval. The resected prostate tissue had higher levels of oxidative DNA damage than leukocytes. We could not assess 8OHdG in the biopsy obtained before the treatment due to the shortage of tissue, so we compared the prostatectomy specimens from our subjects to the tissue from seven similar patients who did not consume our daily tomato sauce dishes. There was a significant difference ($P=0.03$) between the mean 8OHdG/10^5dG ratio in our subjects and controls (0.76 vs. 1.06). These results were confirmed by an 8OHdG histochemical staining method which was used on slides from biopsy and surgical paraffin blocks for each patient [9]. Cancer cells had the highest density staining, hyperplastic cell nuclei varied from none to moderate staining, while stromal nuclei were usually not stained. Microscopic observation scoring by two pathologists found shifts to less staining for each patient from biopsy to the resected tissue slides. The more objective digital image processing also revealed decreased 8OHdG immunodensity of cancer cell nuclei after tomato sauce supplementation ($P<0.01$). The increased intake of tomato products seemed to have antioxidant effects in our subjects, but were the changes in any way affecting the development of malignant cells in their prostates?

Table 1
Tomato sauce supplementation effects in prostate cancer patients

Biomarker	Before intervention	After intervention	No intervention
Serum PSA (ng/mL)	10.9 ± 1.1	8.7 ± 0.9	13.8 ± 2.4
Serum lycopene (nM)	638 ± 60	1258 ± 95	
Prostate tissue lycopene (nmol/g)	0.28 ± 0.045	0.82 ± 0.12	
Leukocyte 8OHdG/10^5dG	0.61 ± 0.05	0.48 ± 0.04	
Prostate tissue 8OHdG/10^5dG		0.76 ± 0.10	1.06 ± 0.17
8OHdG immunodensity (% optical density)	22.1 ± 2.7	13.2 ± 2.7	
Carcinoma apoptotic index (%)	0.84 ± 0.13	2.76 ± 0.58	1.91 ± 0.32

Results are mean ± S.E.
All "after intervention" means are significantly different from the "before intervention" means.
Prostate tissue 8OHdG/10^5dG ratio is significantly lower after intervention when compared to prostatectomy specimens from untreated (no intervention) patients.

Serum PSA was measured before the start and at the end of the treatment. It decreased significantly from 10.9 to 8.7 ng/mL ($P<0.001$). Other randomly selected prostatectomy patients had PSA of 13.8 just before their operation. Serum PSA is not tumor specific and may also increase in cases of prostatitis and BPH. However, it is used in the screening and assessment of the risk of prostate cancer, although recently doubts were raised about the alarm point of 4 ng/mL [10], since in some cases prostate cancer develops without raising PSA above this limit. Usually, lower PSA levels indicate better health of prostate tissue and the significant 17.5% decrease in our subjects seems promising in this respect, consistent with a possible decrease in the number of PSA secreting cells.

In order to test this hypothesis, we investigated the prevalence of apoptosis (by TUNEL assay) in prostate tissue

sections from our subjects, both in hyperplastic and neoplastic cells. The apoptotic index (AI) of cancer areas more than tripled during the supplementation interval, from 0.8% to 2.7%. A comparable group of patients, who did not consume tomato sauce dishes, had 1.9% AI in their prostatectomy specimens [11]. Hyperplastic areas seemed to double their AI during the intervention (from 0.7% to 1.4%), but a similar result (1.4%) was obtained from the prostatectomy tissue of patients who did not consume our tomato sauce dishes. Great variability in the distribution of apoptotic cells for BPH and cancer areas was found in both biopsy and resected prostate tissues, but in five of our subjects among the 26 examined, the AI ranged as high as 4.7%–13.3% for the most apoptotic cell areas after tomato sauce supplementation. Thus, it is possible that tomato sauce intake may induce apoptosis in some tumor cells and arrest cancer progression.

Which of the many phytochemicals in tomatoes could be responsible for the observed apoptotic effects? We turned to cell culture studies of human prostate cancer LNCaP to investigate the cell cycle, viability and apoptosis in the presence and absence of lycopene in the growth medium [12]. Water soluble 10% lycopene beadlets were used as a source of lycopene against placebo beadlets of matched composition. Four levels of lycopene in the culture medium were investigated (0.1, 0.5, 1, and 5 μM), which correspond to 0.1, 0.5, 1 and 5 nmol/mL, to encompass the average lycopene concentration in the serum of our subjects (1.26 μM) and in prostate tissue (0.82 nmol/g) after tomato sauce intervention. Lycopene was absorbed by LNCaP cells during the first 24 h and significantly inhibited their growth at each dose level. Flow cytometry indicated significant cell cycle arrest at a physiologically feasible 1 μM dose. The incidence of apoptosis increased with time in a dose-dependent manner, reaching 20.6% at the highest 5 μM concentration. Similar effects were obtained by other researchers with various lines of human prostate cancer cells (PC-3, DU 145) incubated with 5 μM lycopene [13]. These results are consistent with the data from our subjects and support the role of lycopene as a possible bioactive compound in tomatoes, preventing and controlling the development of prostate cancer [14].

The observed multiple effects of lycopene in prostate physiology demand a specific action on the molecular level of gene expression to explain the mechanism of cell proliferation arrest, apoptosis and the decrease in oxidative stress. Strong support for the bioactive properties of lycopene in prostate health was recently found in animal studies [15,16]. When MatLyLu Dunning prostatic adenocarcinoma cells are injected into the ventral prostate of Copenhagen rats, they quickly develop into lethal tumors. Although laboratory rats absorb lycopene very poorly compared to humans, sufficient amounts (200 mg lycopene/kg diet) were incorporated in their diet during the 4 weeks before tumor cell injection to produce a 1 μM lycopene concentration in plasma, and 0.4 nmol/g in the tumor tissue, after 18 days of tumor growth. The gene chip analysis of tumor tissue revealed that lycopene supplementation upregulated 101 genes and suppressed 261 genes. The most significant was the decrease of steroid 5-α-reductase expression, because of the role of 5-α-dihydrotestosterone (DHT) in prostate cancer development [17]. DHT blocks LNCaP apoptosis in cell cultures [18], which could explain the effect of lycopene on apoptosis in the same cell strain in our study. A whole set of androgen target genes was significantly downregulated in the lycopene-treated group, as well as those for two cytokines, insulin-like growth factor I (IGF-I) and interleukin-6 (IL-6), both implicated in prostate cancer development [19,20]. Two important enzymes generating reactive oxygen species (ROS) exhibited decreased expression, the inducible nitric oxide synthase and NADPH oxidase. Similar supplementation of young healthy rats with lycopene for 8 weeks resulted in a significant accumulation of lycopene in prostate, with an accompanying reduction in the gene expression of inflammatory signaling (cytokines, immunoglobulins and their receptors), IGF-I, and decreased androgen activation. Lycopene did not interfere with normal prostate growth but seemed to modulate the expression of genes crucial to prostate health. These findings should be confirmed by using the same techniques to investigate gene regulation in prostate cancer tissue of human subjects, with concurrent measurement of androgens and lycopene concentrations in prostate and plasma.

A small clinical trial of lycopene supplementation (30 mg/day, tomato oleoresin extract) was conducted on 15 prostate cancer patients, who were compared with 11 unsupplemented cases [21]. The results were mostly inconclusive, because the plasma lycopene levels of supplemented patients did not increase significantly after 3 weeks of treatment. However, the researchers noticed a relative decrease in the extension of prostate cancer to surgical margins and extra-prostatic tissues, as well as in the extent of high-grade prostatic intraepithelial neoplasia (PIN). There is also a startling case report of a patient with metastatic prostate cancer, whose formal treatment, including prostatectomy, was unsuccessful [22]. He entered hospice care and began treating himself with lycopene (10 mg/day) and saw palmetto (900 mg/day) supplements. His PSA decreased from 365 ng/mL to 8 mg/mL within 2 months, stabilizing at 3–8 ng/mL, his bone metastases improved and he was asymptomatic after 18 months of this self-administered supplementation.

Although lycopene appears to be a bioactive compound in cell culture and animal studies, we cannot exclude the possibility of a synergistic action with other phytochemicals in tomato, especially glycoalkaloids (tomatine), phenolic compounds (quercetin, kaempferol, naringenin, and chlorogenic acid), salicylates, and carotenoids other than lycopene (phytoene and phytofluene). Salicylates are well known for their anti-inflammatory action, and quercetin inhibits the prostate androgen receptor [23]. Boileau et al. [24] found a

much greater effect of whole tomato powder diet on rat prostate cancer, induced with *N*-methyl-*N*-nitroso-urea and testosterone, than that of lycopene beadlets. Lycopene content was only 13 mg/kg of tomato powder diet, and as much as 161 mg/kg of beadlet augumented diet. The consumption of tomato powder, but not of lycopene beadlets, inhibited rat prostate carcinogenesis, prolonged survival and reduced mortality, especially in conjunction with 20% caloric restriction, although the effects seemed independent.

In summary, the scientists have just started to unravel the complicated etiology of prostate diseases and their interactions with diet and lifestyle. The possible preventive role of lycopene in reducing the incidence of chronic diseases (cardiovascular pathology, various forms of cancer) has been examined in comprehensive reviews [25–27], and lycopene is included among promising chemopreventive dietary substances [28]. Recently, multiple modes of lycopene action in prostate cancer risk reduction were discussed in an excellent review [29] which stressed the inhibition of inflammation, local androgen signaling, multiple levels of antioxidant defense, and reduction of prostate epithelial cell proliferation, all contributing to improving prostate health. The increased consumption of lycopene containing fruits, vegetables, and especially tomato products, may provide a measure of protection, while complementary therapy with lycopene supplements must await further well-designed clinical trials employing the latest experimental techniques to investigate the most informative physiological indicators.

References

[1] American Cancer Society, Cancer Facts and Figures 2004, National Home Office, Atlanta, GA, USA, 2004, pp. 1–56.

[2] E.D. Crawford, Epidemiology of prostate cancer, Urology 62 (Suppl. 6A) (2003) 3–12.

[3] P.K. Mills, W.L. Beeson, R.L. Phillips, G.E. Fraser, Cohort study of diet, lifestyle and prostate cancer in Adventist men, Cancer 64 (1989) 598–604.

[4] E. Giovannucci, A. Ascherio, E.B. Rimm, M.J. Stampfer, G.A. Colditz, W.C. Willet, Intake of carotenoids and retinol in relation to risk of prostate cancer, J. Natl. Cancer Inst. 87 (1995) 1767–1776.

[5] W. Stahl, H. Sies, Uptake of lycopene and its geometrical isomers is greater from heat processed than from unprocessed tomato juice in humans, J. Nutr. 122 (1992) 2161–2166.

[6] H.C. Furr, R.M. Clark, Intestinal absorption and tissue distribution of carotenoids, J. Nutr. Biochem. 8 (1997) 364–377.

[7] P.H. Gann, J. Ma, E. Giovannucci, W. Willet, F.M. Sacks, C.H. Hennekens, M.J. Stampfer, Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis, Cancer Res. 59 (1999) 1225–1230.

[8] L. Chen, M. Stacewicz-Sapuntzakis, C. Duncan, R. Sharifi, L. Ghosh, R. van Breemen, D. Ashton, P.E. Bowen, Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention, J. Natl. Cancer Inst. 93 (2001) 1872–1879.

[9] P.E. Bowen, L. Chen, M. Stacewicz-Sapuntzakis, C. Duncan, R. Sharifi, L. Ghosh, H.-S. Kim, K. Christov-Tzelkov, R. van Breemen, Tomato sauce supplementation and prostate cancer: lycopene accumulation and modulation of biomarkers of carcinogenesis, Exp. Biol. Med. 227 (2002) 886–893.

[10] I.M. Thompson, D.K. Pauler, P.J. Goodman, C.M. Tangen, M.S. Lucia, H.L. Parnes, L.M. Minasian, L.G. Ford, S.M. Lippman, E.D. Crawford, J.J. Crowley, C.A. Coltman, Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng per milliliter, New Engl. J. Med. 350 (2004) 2239–2246.

[11] H.-S. Kim, P.E. Bowen, L. Chen, C. Duncan, L. Ghosh, R. Sharifi, K. Christov, Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma, Nutr. Cancer 47 (2003) 40–47.

[12] E.-S. Hwang, P.E. Bowen, Cell cycle arrest and induction of apoptosis by lycopene in LNCaP human prostate cancer cells, J. Med. Food 7 (2004) 284–289.

[13] E. Kotake-Nara, M. Kushiro, H. Zhang, T. Sugawara, K. Miyashita, A. Nagao, Carotenoids affect proliferation of human prostate cancer cells, J. Nutr. 131 (2001) 3303–3306.

[14] P.E. Bowen, Is lycopene a likely candidate for prostate cancer prevention and control? AGRO-Food Industry Hi-Tech, 2003 (July–August), pp. 11–15.

[15] U. Siler, L. Barella, V. Spitzer, J. Schnorr, M. Lein, R. Goralczyk, K. Wertz, Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model, FASEB J. 18 (2004) 1019–1021.

[16] A. Herzog, U. Siler, V. Spitzer, N. Seifert, A. Denelavas, P. Buchwald Hunziker, W. Hunziker, R. Goralczyk, K. Wertz, Lycopene reduced gene expression of steroid targets and inflammatory markers in normal rat prostate, FASEB J. 19 (2005) 272–274.

[17] J.D. Debes, D.J. Tindall, The role of androgens and the androgen receptor in prostate cancer, Cancer Lett. 187 (2002) 1–7.

[18] K. Kimura, M. Markowski, C. Bowen, E.P. Gelmann, Androgen blocks apoptosis of hormone-dependent prostate cancer cells, Cancer Res. 61 (2001) 5611–5618.

[19] M. Pollak, Insulin like growth factors and prostate cancer, Epidemiol. Rev. 23 (2001) 59–66.

[20] D. Giri, M. Ozen, M. Ittmann, Interleukin-6 is an autocrine growth factor in human prostate cancer, Am. J. Pathol. 159 (2001) 2159–2165.

[21] O. Kucuk, F.H. Sarkar, W. Sakr, Z. Djuric, M.N. Pollak, F. Khachik, Y.-W. Li, M. Banerjee, D. Grignon, J.S. Bertram, J.D. Crissman, E.J. Pontes, D.P. Wood, Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy, Cancer Epidemiol. Biomark. Prev. 10 (2001) 861–868.

[22] B.R. Matlaga, M.C. Hall, D. Stindt, F.M. Torti, Response of hormone refractory prostate cancer to lycopene, J. Urol. 166 (2001) 613.

[23] N. Xing, Y. Chen, S.H. Mitchell, C.Y. Young, Quercetin inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells, Carcinogenesis 22 (2001) 409–414.

[24] T.W.-M. Boileau, Z. Liao, S. Kim, S. Lemeshow, J.W. Erdman Jr., S.K. Clinton, Prostate carcinogenesis in *N*-methyl-*N*-nitroso-urea(NMU)-testosterone-treated rats fed tomato powder, lycopene or energy-restricted diets, J. Natl. Cancer Inst. 95 (2003) 1578–1586.

[25] A.W. Rao, S. Agarwal, Role of lycopene as antioxidant carotenoids in the prevention of chronic diseases: a review, Nutr. Res. 19 (1999) 305–323.

[26] A.W. Rao, S. Agarwal, Role of antioxidant lycopene in cancer and heart disease, J. Am. Coll. Nutr. 19 (2000) 563–569.

[27] H. Tapiero, D.M. Townsend, K.D. Tew, The role of carotenoids in the prevention of human pathologies, Biomed. Pharmacother. 58 (2004) 100–110.

[28] G.J. Kelloff, J.A. Crowell, V.E. Steele, R.A. Lubert, C.W. Boone, W.A. Malone, E.T. Hawk, R. Lieberman, J.A. Lawrence, L. Kopelovich, I. Ali, J.L. Viner, C.C. Sigman, Progress in cancer chemoprevention, Ann. N.Y. Acad. Sci. 889 (1999) 1–13.

[29] K. Wertz, U. Siler, R. Goralczyk, Lycopene: modes of action to promote prostate health, Arch. Biochem. Biophys. 430 (2004) 127–134.