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FILE: ▪ Lycopene
▪Prostate Cancer
▪Chemoprevention

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RE: Review of Lycopene, Related Compounds, and Their Mechanism of Action

Campbell J, Canene-Adams K, Lindshield B, Boileau T, Clinton S, Erdman JW. Tomato Phytochemicals and prostate cancer risk. *J Nutr.* 2004;134:3486S–3492S.

The top three most prevalent cancers for men in developed countries are lung, prostate, and colorectal cancer. Prostate cancer alone accounts for approximately 30,000 deaths annually in the U.S. It is generally a slow-growing cancer that mainly affects the elderly, and, since the average age of the population continues to increase, strategies to prevent prostate cancer are important public health goals. Recently, lycopene, a carotenoid found in tomatoes (*Lycopersicon esculentum*), watermelon (*Citrullus lanatus*), pink grapefruit (*Citrus* x *paradisi*), apricots (*Prunus armeniaca*), and other fruits, has been studied for its ability to prevent prostate cancer. Tomatoes are the major source of lycopene commercially. Although lycopene is the most abundant carotenoids in tomatoes, they also contain other potentially beneficial carotenoids such as alpha-carotene, beta-carotene, lutein, phytoene, and phtyofluene. Tomatoes also contain appreciable amounts of polyphenols, including quercetin, kaempferol, and naringenin. This article reviews epidemiological, in vitro, and in vivo studies, as well as the potential mechanisms of action for the beneficial effects of tomato carotenoids.

Epidemiological evidence

Currently, 85% of the public's consumption of lycopene comes from canned tomato sauce, which contains 287 micrograms/g lycopene. One 6-year, prospective, epidemiological study of approximately 47,000 men, the Health Professional Follow-up Study (HPFS), concluded that 2 to 4 servings per week of raw tomatoes significantly reduced the risk of prostate cancer by 26% compared to no servings per week. Additionally, eating tomato products such as pizza and tomato sauce 2–4 times per week significantly reduced the risk by 15% and 34%, respectively, compared to not eating these foods. The HPFS study period was extended an additional 6 years. The results supported the early findings, and concluded that "tomato sauce consumption was associated with a 23% reduction in prostate cancer risk when two or more

servings were compared with <1 serving per week." Subgroup analysis revealed an inverse association between serum lycopene concentration and prostate cancer risk, which was most evident in men older than 65 years and in those with no family history of prostate cancer. The authors conclude from the HPFS studies, "tomato and lycopene intake may demonstrate stronger protection in cases of sporadic prostate cancer rather than in cases with a strong genetic component."

In vitro and in vivo animal studies

The authors tested the antiproliferative effect of tomato polyphenol on LNCaP, a human prostate cancer cell line, and on Hepa1c1c7, a mouse hepatocyte cell line. Polyphenols can be attached to a molecule of sugar, in which case they are in the "glycone" form. When the polyphenol is not attached to a molecule of sugar it is said to be in the "aglycone" form. Both cell lines were inhibited in a dose-dependent manner (10–50 micromol/L) by the aglycone forms of quercetin, kaempferol, and naringenin, but not as glycones. Interestingly, treating the cell lines with a combination of the aglycone polyphenols (25, 40 and 50 micromol/L total) produced greater inhibition than treating them with the aglycone polyphenols individually, suggesting a synergism exists between the polyphenols.

Supporting the hypothesis that a synergism might exist between the chemicals, researchers in the same laboratory studied the effects of tomato powder versus lycopene alone on a prostate cancer rat model. They fed rats diets of 10% tomato powder, 0.025% lycopene, 20% dietary energy restriction, or control rats allowed to eat ad libitum. Rats fed the tomato powder had a significant 26% decrease in prostate cancer-specific mortality, while the lycopene-fed rats had a nonsignificant 9% decrease in mortality. Rats on the caloric restricted diet had a decreased in prostate cancer-specific mortality by 32% compared with the rats fed unrestricted amounts of food. When they segmented their data into 45-week intervals, energy restriction diets decreased the risk of prostate cancer by 48% during the first 45 weeks, but had not effect after 45 weeks. Tomato powder and lycopene had a nonsignificant effect during the first 45 days, but decreased the risk of prostate cancer by 56% and 44%, respectively, after 45 weeks.

Human clinical trials

Although the role of all carotenoids in humans has yet to be fully determined, "25 carotenoids and 9 metabolites have been identified and characterized in human serum; breast milk; and several organs, including the breast, lung, liver, cervix, colon, skin, and prostate." Of all the organs studied, the prostate contains the highest concentration of lycopene. Lycopene occurs in two forms—*cis* and *trans*. Tomato and its products contain primarily all-*trans*-lycopene (79–91%); however, "*cis*-lycopene accounts for 79-88% of total lycopene in malignant and benign prostate tissues." In vitro experimentation demonstrated that *cis* lycopene is absorbed more readily than all-*trans*-lycopene. The role of *cis* versus *trans* lycopene in human physiology has not yet been determined.

In a trial of 32 men with diagnosed prostate cancer, supplementation with 30 mg/d tomato sauce resulted in a tripling of total lycopene in the prostate. Two other studies concluded that

dietary intervention and supplementation with "15 mg lycopene and smaller quantities of other tomato carotenoids, including phtyoene, phytofluene, ζ-carotene, and γ-carotene" twice daily positively altered serum markers of prostate cancer progression. Serum prostate-specific antigen (PSA) levels, a marker of tumor activity, decreased in both trials, and "tomato oleoresin supplementation altered biomarkers of cell growth and differentiation" in the one study in which it is was tested. The authors of this review article did not report whether the altered differentiation was in the direction of more or less differentiation. Cancer cells show a decrease in cellular differentiation, and are sometimes said to "revert back" to a more undifferentiated, embryonic-type cell. If tomato carotenoids can increase cellular differentiation, they may be important in the treatment of prostate cancer.

Potential mechanisms of action

There are five mechanisms that researchers propose may account for the beneficial effects of tomato phytochemicals and their metabolites. These mechanisms may complement each other and have overlapping functions.

Lycopene is the strongest antioxidant compared with "other commonly consumed carotenoids." Decreased DNA damage has been reported in white blood cells after 15 days of supplementation with tomato and tomato juice. Second, lycopene alters the biotransformation of xenobiotics, which are pharmacologically, endocrinologically, or toxicologically active substances not produced by the body that must be metabolized to a different compound before being eliminated in the stool or urine. Xenobiotics are metabolized by two families of enzymes, called cytochrome P450 enzymes, via two pathways, called phase I and phase II detoxification pathways. The authors report results which showed lycopene significantly induced phase I enzymes in a dose-dependent manner and doubled hepatic quinone reductase (QR), a phase II enzyme. Tomato flavonoids also affect these enzyme systems. Kaempferol and naringenin inhibit the cytochrome P450-IA enzyme, while quercetin inhibits this same enzyme while also increasing QR activity.

Cooked tomatoes and lycopene alone alter "hormone and growth factor signaling in prostate cells." This includes alterations in insulin-like growth factor-1 (IFG-1) activity. IFG-1 stimulates cellular proliferation and decreases apoptosis, which is a mechanism by which normal cell death happens. Cancer cells are said to be immortal—they proliferate indefinitely. Eating cooked tomatoes was associated with a 31.5% decrease in serum IGF-1 levels in a case-controlled study of 112 men. Beneficial alterations of IGF-1 concentrations or its ability to stimulate cell division have also been found in rats and in healthy men. The authors report an in vitro study in which "lycopene and tomato polyphenols, including quercetin, kaempferol, and rutin, were shown to interfere with IGF-1 signaling...thus preventing the growth factor from stimulating cell proliferation."

In a number of cancer cell lines, including breast cancer cells, endometrial cancer cells, and in normal prostate cells, lycopene halted cellular replication in vitro. Lastly, lycopene and its metabolites may help fight some cancers by increasing connexin 43 levels. Connexin 43 is a molecule involved in cell-to-cell communication, "which is important in the regulation of uncontrolled, rapid cell growth." In a metastatic prostate cancer cell line (PC-3MM2),

lycopene did not increase connexin 43; however, it did in another prostate cancer cell line (PC-3), a breast cancer cell line (MCF-7), and oral cancer cells (KB-1). The inhibition of connexin 43 in these cell lines was associated with an inhibition of cell growth, suggesting that upregulation of connexin 43 may be important to the anticancer action of lycopene.

Strong epidemiological and experimental evidence exists to support the beneficial effects of tomatoes, tomato products, and isolated tomato phytochemicals on prostate health. Primary prevention of prostate cancer by consuming these products appears well-supported by the evidence reported in this review article. Some in vitro data supports the hypothesis that tomato phytochemicals may be useful in the treatment of cancers; however, no in vivo trials were reported that support this. Since a synergistic effect appears to exist between tomato phytochemicals, recommending the consumption of supplements made from whole tomatoes and/or the consumption of 2 to 4 or more servings per week of tomatoes and tomato products may reduce the incidence of prostate cancer and health care costs in our aging population.

—John Neustadt, ND

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