Introduction

The association between high fruit and vegetable intakes and reduced risk of certain diseases, including cancer is consistently strong. These dietary constituents are known to contain high levels of antioxidants, and oxidative stress is recognized as one of the major contributors to increased risk of cancer. The carotenoid family of antioxidants, especially beta-carotene, has received particular attention for their inhibition of active oxygen and radical formation. It has been shown through epidemiological approaches and laboratory studies that regular intake of tomatoes lowers the risk of several major types of cancer. Animal models have confirmed this by showing a reduction in prostate, breast and digestive tract tumor proliferation. The active antioxidant in tomatoes is lycopene, an acyclic hydrocarbon that lacks provitamin A activity but has high oxygen quenching ability. Surprisingly, cooking does not disrupt lycopene and actually increases its bioavailability by releasing it from tomato membrane and fiber that inhibit lycopene absorption. This paper looks at the research findings associated with the emergence of lycopene as an antioxidant that may help to reduce oxidative stress and cancer risk.

Characteristics of Lycopene

Carotenoids act as light-absorbing pigments in photosynthesis and are responsible for the bright colors of various fruits and vegetables. Carotenoids are tetraterpenes formed by tail-to-tail linkage of two C-20 units and have an extended system of conjugated double bonds. The hydrocarbon carotenoids alpha- and beta-carotene are widely used as sources for vitamin A, but lycopene lacks their beta-ionone ring structure and does not have provitamin A activity (1). Lycopene is an acyclic carotenoid containing 11 conjugated double bonds arranged linearly in the all-trans form. In nature most carotenoids occur in the all-trans form, which is thermodynamically more stable than the cis- form. This allows carotenoids to undergo trans to cis isomerization if induced by chemical reactions or exposed to light within their absorption range (1).

Carotenoids are transported in the blood by lipoproteins and appear to concentrate in tissues with a large number of LDL receptors and a high rate of lipoprotein uptake, such as the adrenals, testes, liver, kidney, and prostate. Lycopene analysis of plasma and tissue samples obtained at autopsy from 16 subjects (2) indicated that lycopene concentrations superceded other common carotenoids in the testes and adrenals. Another autopsy study showed that beta-carotene and lycopene were the predominant carotenoids in the liver, kidney, and lung tissue (3). A third study (4) found that lycopene was a predominant carotenoid in the human prostate and in a mouse model with implants of human prostate adenocarcinoma.

Antioxidant Properties

Carotenoids such as lycopene convert singlet state oxygen to its ground triplet state by absorbing and then dispersing excess excited state energy in the form of heat (1). Singlet oxygen can react with unsaturated compounds such as polyunsaturated fatty acids but may be intercepted by physical quenching. Lycopene has an exceptionally high singlet oxygen quenching ability, twice that of beta-carotene. Thus, tissues may be spared from oxidation by the in vivo oxidation of lycopene. Lycopene also interacts with other active oxygen species, such as hydrogen peroxide, which can generate the hydroxy radical known to induce strand scission in DNA (5) and nitrogen dioxide, an air pollutant causing cell membrane damage (6). These changes may promote DNA mutations conducive to tumor generation and membrane alterations that allow for proliferation and metastases. If lycopene does act as an antioxidant in vivo, elevation of plasma lycopene after dietary intake of lycopene-containing foods should produce an increase in plasma concentrations of lycopene metabolites. When compared to a placebo treatment containing no lycopene (7), lycopene-containing treatments showed a significant increase in cyclolycopene, an oxidative metabolite of lycopene.

Another study (8) more clearly shows the aforementioned in vivo antioxidant potential of lycopene. Lipid oxidation (malondialdehyde) was measured by thiobarbituric acid (TBA)-malondialdehyde assay and reported as TBA-reactive substances (TBARS). Protein oxidation was measured by loss of reduced thiol groups and DNA oxidation was measured by 8-oxodG analysis, an important indicator of DNA oxidation that has been elevated in cancerous tissues. All lycopene treatments resulted in significantly lower serum TBARS than in the placebo group and although not statistically significant, a tendency toward lowered

protein and DNA oxidation was observed. Lycopene, being a lipid-soluble antioxidant, may have provided greater protection to lipid molecules than to proteins and DNA. Tomato juice, spaghetti sauce, and tomato oleoresin were used to provide dietary lycopene in amounts equivalent to 1-2 servings per day, an amount that is easily achievable and in keeping with current dietary recommendations pertaining to healthy eating. This is a departure from other studies (7,9) that have administered levels of lycopene realistically unattainable without supplementation.

Food Sources and Bioavailability

In contrast to more widespread carotenoids, lycopene predominantly occurs in fresh tomatoes and tomato products such as tomato catsup, tomato juice, tomato sauce, and tomato paste (1). This has made it convenient to accurately measure lycopene intake, absorption and plasma serum concentrations and some interesting trends have been observed. One of the first lycopene studies found that bioavailability can be increased two- to threefold by ingesting tomato juice heated with corn oil as compared to unprocessed juice (10). This may be attributable to the extraction of lycopene into the lipophilic phase during the boiling process, where carotenoids are known to be readily absorbable. In a similar study (11), lycopene bioavailability from a single dose of fresh tomatoes or tomato paste ingested together with 15g corn oil was compared by analyzing carotenoid concentrations in the chylomicron fraction. Total lycopene content in the fresh tomatoes and tomato paste were similar but the total lycopene chylomicron response was 3.8 fold higher after ingestion of tomato paste as compared to fresh tomatoes. Cooking or chopping are believed to enhance carotenoid accessibility and bioavailability by breaking down sturdy cell walls. Another study (12) also found consumption of tomato sauce and not fresh tomatoes or tomato juice to be the strongest predictor for higher lycopene serum concentrations.

With the current popularity of vitamin supplements and the antitumorigenic properties of high doses of lycopene, the findings of another study (7) are noteworthy. A crossover trial studied the bioavailability of lycopene from tomato juice and 2 dietary supplements each containing 70-75 mg of lycopene. Plasma lycopene concentrations during tomato juice, oleoresin, and lycopene beadlet ingestion were not significantly different, but all were higher than during placebo ingestion. Thus, lycopene supplements appear to be as effective and bioavailable for increasing plasma lycopene concentrations as is tomato juice.

Epidemiological Evidence for Lycopene in Cancer Prevention

Some of the first evidence for lycopene's role in cancer prevention came in a case-control study of digestive tract cancer in Iranian males (13), which found that consuming at least one tomato per week showed a 40% risk reduction in esophageal cancer. The Mediterranean diet, often correlated with lower rates of cancer and heart disease due to certain dietary patterns, exhibits regional specification in tomato consumption. This allowed for another case-control study that estimated dietary intakes of fruits and vegetables in low-risk versus high-risk cancer populations in Italy. Higher tomato consumption was shown to be particularly effective in reducing the risk of gastric cancer (14). Furthermore, a different study (15) also conducted in northern Italy found tomatoes to have a consistent protective effect on cancers of the digestive tract, most notably gastrointestinal neoplasms. The highest quartile of tomato intake, at least seven servings per week, was associated with odds ratios between 0.4 and 0.7 as compared to the lowest intake quartile. Similar regional variation in diet was used in a cross-sectional study (16) in four areas of Japan with different rates of stomach cancer. The researchers investigated possible lifestyle factors associated with stomach cancer mortality using assays for the micronutrients vitamin A, vitamin C, vitamin E, B-carotene, and lycopene in plasma. Lycopene was singled out as the only nutrient having a strong inverse correlation with stomach cancer.

Recent analysis of the US Health Professionals Follow-up Study, which related a dietary questionnaire to the incidence of prostate cancer (11), showed an inverse association between high intake of tomato products and prostate cancer risk. It was shown that lycopene intake, but not the overall intake of fruit and vegetables, was inversely related to prostate cancer risk. Tomato products such as tomato sauce, tomatoes, and pizza showed the strongest association but no relationship was found for unprocessed tomato juice, which has a lower bioavailability of lycopene. Additionally, 14,000 male Seventh-day Adventists were used to relate dietary and lifestyle factors to subsequent risk of prostate cancer during a follow up of 6

years. Among dietary factors, consumption of five or more tomato servings per week was associated with a significantly decreased risk of prostate cancer (17).

Correlations for lycopene and pancreatic cancer have been drawn by comparing previously donated stored frozen serum samples from pancreatic cancer patients with those of donated samples from matched controls (18). Analysis of retinol, RBP, B-carotene, lycopene, a-tocopherol and selenium found the greatest difference in mean serum concentrations between cases and controls for lycopene (0.70 +/- 0.07 umol/L vs. 0.93 +/- 0.06 umol/L), possibly implicating decreased plasma levels of lycopene in pancreatic cancer. It should be noted that there are numerous other epidemiological studies looking at lycopene intake or concentrations as part of carotenoid or fruit and vegetable intake. Many of these indicate that risks for various types of cancer increase with decreasing values of lycopene, although some results are just shy of statistical significance.

Animal Studies of Lycopene on Tumor Proliferation

The direct effects of lycopene on tumor proliferation has been examined in endometrial, mammary, and lung human cancer cells (19). When delivered in cell culture mediums, lycopene was a more effective cell growth inhibitor than alpha-carotene or beta-carotene. Lycopene required smaller concentrations for inhibition and the inhibitory effect of lycopene was detected after 24 hours of incubation, while alpha- and beta- carotene required two to three day incubations. The carotenoid inhibitory effect will reverse if the lycopene concentrations are not maintained by daily addition of lycopene, because the half-life of carotenoids is 12-20 hours. This suggests that frequent consumption of lycopene is most effective for tumor suppression. The suppression of cell growth was secondary to its inhibition of DNA synthesis, as evidenced by reduced incorporation of tritiated-H into the cells. Different lycopene preparations, including synthetic material, tomato extracts and purified samples, all caused cell growth inhibition, strongly pointing to lycopene or its metabolite as the effective inhibitor. Mechanistically, lycopene was found to interfere with IGF-I induced growth stimulation of endometrial and breast cancer cells. This effect was dose-dependent and lycopene was able to abolish the effect of the IGF-I growth factor.

The effects of chronic ingestion of lycopene on the development of spontaneous mammary tumors was examined in two groups of high mammary tumor strain SHN virgin mice (20). A diet supplemented with lycopene delayed and suppressed mammary tumor development, but was associated with a higher number of preneoplastic mammary hyperplastic alveolar nodules (HAN) which may reflect a protective role due to stimulation of cell differentiation. In the experimental group, there were also decreases in mammary gland activity of thymidylate synthetase, an enzyme of cell division, and serum levels of free fatty acid and prolactin. The latter is especially significant because prolactin stimulates mammary cell division, which provides favorable conditions for tumor development. An DMBA-induced rat mammary tumor model was used to compare the effect of lycopene-enriched tomato oleoresin with beta-carotene on the initiation and progression of mammary tumors. Rats were injected with lycopene-enriched tomato oleoresin or beta-carotene for two weeks prior to tumor induction by DMBA and for four months after carcinogen administration. HPLC analysis showed that both carotenoids were absorbed into blood, liver, mammary gland, and mammary tumors. The tomato oleoresin-treated rats developed fewer tumors, and the tumor area was smaller than that of the unsupplemented rats (21).

The effects of tomato juice on urinary bladder carcinogenesis were studied in rats initiated with a carcinogen (9). The multiplicity, but not incidence, invasion or differentiation, of transitional cell carcinomas (TCCs) was decreased in the experimental group given tomato juice. However, there was no influence on the incidence of simple and nodullopapillary hyperplasias and the tomato juice was administered in doses beyond normal human consumption. This experiment may not be as clear because tomato juice was used instead of pure lycopene and vitamin C in combination with salts has been found to actually enhance rat urinary bladder carcinogenesis. In a study on the inhibition of colon carcinogenesis in rats (22), it was found that tomato juice was more effective than pure lycopene in reducing tumor incidence, despite essentially equal lycopene dosages. It may be likely that other micro-constituents in tomato juice may combine with lycopene to inhibit colon tumor development. It was also determined that a higher lycopene dosage conveyed a greater protective effect. Lycopene was found to accumulate in the colonic mucosa at higher lycopene dosage and in the liver regardless of dosage. Lycopene levels in the

serum were low or undetectable, which is consistent with previous findings in rats (23) that lycopene is found in the blood within 4-8 hours after a single dose and is eliminated rapidly.

Conclusion

Various conditions, including cardiovascular disease, age-related macular degeneration, and Parkinson's disease have been studied in relation to lycopene (1). However, the most compelling evidence has related tomato products and lycopene intake to a reduction in various common types of cancer. However, ingestion of tomato juice results in significantly increased plasma concentrations of carotenoids other than lycopene (7), so it is unclear whether lycopene or other tomato constituents are entirely responsible for the observed protective effects of tomato-based products reported in epidemiological studies. Furthermore, a high intake of tomatoes rich in lycopene could just be an indicator of a generally healthy life style. It is likely that a combination of antioxidants, as would be found in a diet containing a variety of fruits and vegetables, confers the best protection against oxidative stress and cancer.

As of yet, no prospective intervention trials in humans have been performed to investigate the effect of lycopene supplements on the prevention of cancer development. Since these supplements are available, this would be a logical next step to provide causal evidence for lycopene's role in cancer prevention. Studies on lycopene bioavailability have yielded interesting results that may impact our notions of vitamin absorption and utilization. Losses of lycopene during food production are minimal and cooking tomatoes and consuming them with other foods may actually increase bioavailability. Thus, consumers who prefer pizza sauce, tomato catsup, and marinara sauce over fresh tomatoes should take comfort in the fact that processed tomato products may confer as much lycopene activity as do fresh tomatoes. Lycopene supplements or the addition of lycopene to multivitamins may also provide similar antioxidant properties in areas where tomatoes are unavailable.

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