Can the Consumption of Tomatoes or Lycopene Reduce Cancer Risk?

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Lycopene, a natural antioxidant found predominantly in tomato products, is attracting attention as a cancer prevention agent. Serum and dietary lycopene levels have been found to be inversely related to the incidence of several types of cancer, including prostate cancer. Although the antioxidant properties of lycopene are thought to be primarily responsible for its apparent beneficial effects, other mechanisms may also be involved. We outline the possible mechanisms of action of lycopene and review the current findings of *in vitro* and *in vivo* studies in cancer prevention and to some extent treatment. We examine the epidemiologic evidence regarding consumption of tomato and tomato products with the risk of cancer at various sites. Data suggest lycopene may account for or contribute to chemoprevention, but this hypothesis requires further study. Numerous other potentially beneficial compounds are present in tomatoes and complex interactions among multiple components may contribute to the anticancer properties of tomatoes.

Age-adjusted cancer incidence rates have been reported to be increasing in the United States, although trends vary according to types of cancer.[1,2] Scientists agree that one way people get cancer is through repeated long-term contact with one or more cancer-causing agents, carcinogens. Such agents include tobacco, sunlight, x-rays, and certain chemicals that may be found in air, water, food, drugs, and the workplace.[2] It is estimated that 35% of all cancers are directly associated with diet; another 30% are directly related to smoking.[2] Tobacco smoking is implicated in cancers of the lung, pancreas, bladder, and kidney.[2,3] Various dietary components may increase or decrease the risk of cancer. A high fat intake is associated with an increased risk for cancer of the colon, breast, lung, prostate, rectum, and endometrium.[4,5] These cancers are also associated with obesity, as are cancers of the breast, kidney, cervix, and thyroid.[6,7] The American Cancer Society has recommended that efforts be made to reduce the fat in the typical American diet to no more than 30% fat (percentage of total calories). On the other hand, an increased fiber intake has been found to reduce the risk of colon cancer presumably because it speeds up elimination of waste through the bowels.[8] There is fairly consistent epidemiological evidence that people who consume a diet rich in fruits and vegetables have a lower risk for a variety of cancers. Block et al.[9] reviewed the relationship between fruit and vegetable consumption and cancer risk from more than 200 case control or cohort studies. Among the 156 studies that had calculated the relative risk by comparing the highest versus the lowest intakes of fruit and vegetables, 128 revealed statistically significant risk reductions of various cancers. Analyzed by site, 24 of 25 studies demonstrated a reduced risk for lung cancer, 26 of 30 for cancer of the pancreas and stomach, 23 of 38 for colorectal and bladder cancer, 28 of 29 for cancers of the esophagus, oral cavity, and larynx, and 11 of 13 for cancer of the cervix, ovary, and endometrium. Subsequent population studies continue to verify this association. The chemopreventive substances in fruits and vegetables have not been identified, although there are a number of candidates. Some specific groups of vegetables have been associated with risk reduction. For example, members of the plant genus *Brassica*, including broccoli, cabbage, and Brussels sprouts, appear to protect against various cancers, especially lung cancer.[10] Onions and garlic, from the plant genus *Allium*, appear beneficial toward stomach cancer.[11] Tomato products appear to be associated with a lower prostate cancer risk, possibly because of their high content of lycopene, one of the carotenoids, and similar in structure to β-carotene.[12] The carotenoids have been a focus of research for more than a decade concerning their beneficial or detrimental role in the modulation of carcinogenesis. One of the carotenoids, β-carotene, has been a disappointment, with the publication of clinical trials showing increased risk for lung cancer among current smokers. Another carotenoid, lycopene, continues to be the subject of a National Cancer Institute program

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for the prevention of prostate cancer with the expectation of launching clinical trials.

In a literature review conducted by Giovannucci,[13] 57 associations between higher tomato intake or blood lycopene levels and decreased risk of cancer were found. Of these associations, 35 were statistically significant. The benefit was strongest for prostate, lung, and stomach cancers, although protective associations were also found for cancers of the pancreas, colon, rectum, esophagus, oral cavity, breast, and cervix. Because the data were from observational studies, a cause-and-effect relationship cannot be firmly established. However, the consistently lower risk of cancer associated with higher consumption of lycopene-containing tomatoes provides a strong foundation for further research on lycopene or other substances in tomatoes. This report suggests that lycopene or lycopene in combination with other substances in tomatoes may be a viable bioactive compound in the prevention of some cancers. Therefore, it is worthwhile reviewing what is known about tomatoes and lycopene as a background for evaluating unfolding research in cancer prevention and treatment.

Carotenoids as Candidates for Anticarcinogenic Factors in Fruits and Vegetables

Carotenoids are a class of more than 600 natural pigments that are present in fruits and vegetables and other plant products.[14] Of these, lutein and β-carotene are the most widespread in vegetables and fruits, and their serum concentrations in humans are relatively good markers for fruits and vegetable intake.[15] In the United States, carrots, cantaloupes, broccoli, spinach, greens, vegetable soups, and mixtures are the most abundant sources of β-carotene.[16] In tropical countries, mangoes, papaya, and red palm oil are important sources.[17] β-carotene especially has received tremendous research interest because it is found in relatively high concentrations in human blood.[18] Both in vitro and animal studies have shown that β-carotene is an effective antioxidant by scavenging certain reactive oxygen species, especially peroxyl radical and singlet oxygen. This antioxidant activity appears to be greatest at low oxygen tension[19,20] and is protective against cancers of the skin and oral cavity in mice and hamsters, respectively.[21] However, 6 large-scale human clinical trials have failed to confirm any cancer protective effects of β-carotene. Two of the trials involving heavy smokers showed a significant 18% increase in lung cancer among the smokers who took β-carotene.[22,23] One very large trial involving 22,071 American physicians showed no benefits and no harm from 12 years of supplementation with 50 mg of synthetic β-carotene every second day.[22] Although the results of observational studies seem to suggest that intake of foods rich in β-carotene (i.e., fruits and vegetables) protects against cancer, clinical trials have not found β-carotene to be protective, and in some cases have even shown a negative effect. This suggests that substances in fruits and vegetables or carotenoids other than β-carotene, or in concert with it, may be important in preventing cancers of various types. Tomato products are widely consumed in the United States and hold a prominent place in U.S. vegetable consumption. Lycopene is the predominant carotenoid in tomato products. Blood lycopene concentrations are often higher than any other carotenoid.[24,25]

Cancer Prevention Through Antioxidant Activity

Many mechanisms have been associated with the chemopreventive actions of carotenoids. As part of our normal cell activity, highly reactive free radicals can cause DNA damage. DNA damage to dividing cells causing point mutations is a necessary step at various points between initiation and neoplasm.[26] Carotenoids may neutralize free radicals by acting as antioxidants. Lycopene has the highest antioxidant capacity of the carotenoids.[27] The general structure of lycopene is an aliphatic hydrocarbon with 13 conjugated carbon-carbon double bonds, making it soluble in fats and lipids and also imparting its red color. Its highly conjugated structure is an effective scavenger of reactive oxygen species and the nitrogen dioxide radical. The major difference between β-carotene and lycopene is that β-carotene is the main precursor for vitamin A in the diet whereas lycopene has no pro-vitamin A activity[28] because it is lacking the β-ionone ring structure of β-carotene.

Tinkler et al.[29] studied the quenching of singlet oxygen by β-carotene, astaxanthin, lycopene, and canthaxanthin bound to the surface of lymphoid cells and found that all 4 carotenoids protected the cells against the photodynamic reaction sensitized by mesotetra(4-sulphonatophenyl)porphine, and the highest protection was given by lycopene. It has also been shown that β-carotene and lycopene are effective protectors of lymphocyte cells from nitrogen dioxide radical damage, but lycopene is at least twice as effective as β-carotene.[30] Ribaya-Mercado et al.[31] showed that when skin is subjected to ultraviolet light stress, more lycopene is destroyed than β-carotene, suggesting a role for lycopene in mitigating oxidative damage in tissues exposed to light. Strong interaction of lycopene has been shown to occur with other active oxygen species such as hydrogen peroxide, which can generate the hydroxyl radical known to induce strand

scission in DNA,[32] and nitrogen dioxide, which can cause cell membrane damage.[30] Lycopene was twice as active as β-carotene in the radical scavenging of singlet oxygen[33] and peroxyl radicals.[34]

Human supplementation studies have shown that tomato products or lycopene can act as an *in vivo* antioxidant to protect DNA from damage. Riso et al.[35] found that the daily consumption of 60 g tomato puree per day, containing 16.5 mg lycopene and 0.6 mg β-carotene, for 3 weeks, increased lycopene plasma concentration by 150%. Also, lymphocyte DNA damage after *ex vivo* treatment with hydrogen peroxide decreased by 42% after consumption of the tomato diet. The same investigators found that the consumption of 25 g tomato puree per day, containing 7 mg lycopene and 0.3 mg β-carotene, for 2 weeks, increased plasma lycopene concentration by 323% and decreased DNA damage in lymphocytes to half that of the basal level.[36] These results indicate that a small amount of tomato puree added to the diet over a short period can increase lycopene concentrations and the resistance of lymphocytes to oxidative stress. Rao and Agarwal[37] conducted a study with 19 healthy human subjects to evaluate the uptake and *in vivo* antioxidant properties of lycopene. All subjects completed all 6 treatments including placebo, tomato juice (50.4 mg lycopene/day), 2 types of spaghetti sauce (20.5 or 39.2 mg lycopene/day), and 2 levels of lycopene as tomato oleoresin (75 or 150 mg lycopene/day) for 1 week each. They found that all lycopene treatments significantly lowered serum thiobarbituric acid reactive substances compared to the placebo group, suggesting an *in vivo* protection against lipid peroxidation. There was a tendency toward less DNA damage in a dose-dependent manner in the treatments with spaghetti sauce and tomato oleoresin. These results indicate that lycopene is readily absorbed from tomato products and may act as an in vivo antioxidant to protect from DNA damage.

Although the protection of LDL lipid from peroxidation is not directly tied to cancer prevention, its measurement has been used to demonstrate *in vivo* antioxidant activity of various dietary antioxidants. The carotenoids and lycopene have been the subject of numerous investigations, with mixed results. Bub et al.[38] conducted a human intervention study with 23 healthy men. This study lasted for 8 weeks, with a 2-week low-carotenoid period followed by daily consumption of 330 mL tomato juice, then by 330 mL carrot juice, and then by 10 g of spinach powder, each for 2 weeks. Tomato juice consumption for 2 weeks reduced lipid peroxidation by 18% in these men. Carrot juice and spinach powder had no effect on lipid peroxidation. However, Sutherland et al.[39] found no increased resistance to LDL oxidation with tomato juice supplementation compared to orange juice supplementation in 15 kidney graft patients. Dugas et al.[40,41] examined the effects of *in vivo* and *in vitro* supplementation of carotenoids on LDL oxidation using human aortic endothelial cells (EaHy-1) as the oxidizing agents. They found that *in vitro* enrichment of LDL with lycopene enhanced lipid peroxidation, whereas β-carotene was protective. In human supplement studies where 15 mg β-carotene or 34 mg lycopene were supplemented for 4 or 3 weeks, respectively, β-carotene but not lycopene protected endothelial cell mediated LDL oxidation. These data suggested that lycopene may not be acting as a lipid antioxidant *in vivo*.

Cancer Studies

Antioxidant activity is not the only proposed chemopreventive activity of lycopene. Other functions have been explored in cancer studies via cell culture, animal studies, and human biomarkers studies.

Cell Culture Studies

Because most work has concentrated mainly on anticarcinogenic activity of β-carotene, few studies have focused on the effects of lycopene in cultured cells. Using normal rat liver cells exposed to carbon tetrachloride, it could be shown that the addition of lycopene and other carotenoids reduced cell injury and improved survival of hepatocytes. Lycopene also appeared to suppress lipid peroxidation as shown by reduced formation of malondialdehyde.[42] Lycopene, as well as β-carotene, showed a protective effect against the liver tumor promoter microcystin-LR in mouse hepatocytes. Levy et al.[43] demonstrated that lycopene inhibits mammary, endometrial, and lung cancer cell growth in a dose-dependent manner ($IC_{50} \approx 2$ μM). Karas et al.[44] found that the inhibitory effects of lycopene on MCF-7 (human mammary cancer cells) growth were not accompanied by apoptotic or necrotic cell death. However, lycopene treatment was accompanied by reduction in insulin-like growth factor I receptor signaling, AP-1 transcription factor activation, and cell cycle progression. These findings suggest that the inhibitory effects of lycopene on MCF-7 cell growth are related to interference with the signaling pathway. Nahum et al.[45] also found that lycopene inhibition of human breast and endometrial cancer cell (MCF-7) growth was associated with inhibition of cell cycle progression at the G_1 phase. Lycopene treatment inhibited cell cycle progression via reduction of the cyclin D level. Cyclin D is a known oncogene and a key element in cell cycle progression. It is overexpressed in several cancer cell lines and tumors, especially breast cancer.[46] Thus, reduction of cyclin D by lycopene treatment may contribute

to its proposed action in prevention of breast and prostate cancer.

Matos et al.[47] investigated the effect of lycopene on lipid peroxidation and on the formation of 8-hydroxy deoxyguanosine (8-OHdG), an oxidative DNA damage product, in CV1-P monkey cells exposed to ferric nitrilotriacetate plus ascorbate, which produces hydroxyl free radicals. Cells supplemented with lycopene (20 pmol/10^6 cells) showed an 86% reduction in lipid peroxidation and a 77% reduction in 8-OHdG/dG ratios. These results indicate that lycopene can protect mammalian cells against membrane and DNA damage and possibly play a protective role against tumor promotion associated with oxidative damage.

It was suggested that gap junction communication (GJC) is involved in the growth and control of precancerous cells.[48] Tumor promoters such as phorbol esters are efficient inhibitors of GJC, whereas other compounds such as carotenoids and retinoids induce GJC.[49] Krutovskikh et al.[50] found that α-carotene and β-carotene, as well as lycopene, given at a dose of 50 mg/kg body weight daily in rats inhibited GJC between their liver cells, whereas similar treatment with 5 mg/kg body weight caused enhancement, especially in the β-carotene and lycopene treated groups. At the dose of 0.5 mg/kg body weight, the 3 compounds had no effect. These results show that all 3 agents differentially modulate GJC depending on the dose, with beneficial effects on cell communication only detected at the dose of 5 mg/kg body weight. In human fetal skin fibroblasts, lycopene stimulated GJC at a level of 0.1 μM whereas at least 1 μM of acycloretinoic acid, a possible metabolite of lycopene, was needed to achieve a comparable effect.[49] The biochemical mechanisms responsible for the control of GJC by carotenoids are not fully known, but biologically active metabolites of carotenoids are at least in part responsible for this effect.[50]

The following cell culture and animal studies point to a direct function in the mechanisms of cell cycle, intracellular communication, and/or specific protection from oxidative DNA damage.

Animal Studies

Lycopene has been shown to suppress tumor development in the spontaneous mammary tumor model at one single extremely low dose of lycopene of 0.05 g/kg in the diet.[51] The administration of lycopene to female rats at doses ranging from 0.001 to 0.1 g/kg/day for 2 weeks significantly suppressed mammary tumor development and was associated with a decrease in the mammary gland activity of thymidylate synthetase, as well as a suppression of serum free fatty acid and prolactin concentrations.[51] However, some studies have failed to demonstrate any anticancer efficacy for lycopene in the liver, colon, breast, urinary bladder, or lung.[52-55] Narisawa et al.[52] found that although lycopene itself did not inhibit rat colon carcinogenesis, tomato juice was effective. Okajima et al.[55] demonstrated bladder carcinogenesis suppression effects only when lycopene was combined with β-carotene. Cellular proliferation analyzed by immunohistochemical staining of the proliferative cell nuclear antigen showed that β-carotene or lycopene alone had no effect whereas lycopene combined with β-carotene reduced proliferation. Thus, in animal studies, there are conflicting data with regard to the biological effects of lycopene as a chemopreventive agent.[56] Animal studies are problematic because lycopene is poorly absorbed by rodents and high doses must be fed to produce tissue levels comparable to humans.[57]

Human Studies

There have been more than 100 published human population studies that have addressed lycopene or tomato intake and cancer risk. Studies measured tomato product or lycopene consumption, or plasma lycopene concentrations. These studies can be divided into case control studies, in which the cancer case is identified and a control is sought and data about diet are collected retrospectively, or cohort studies, in which data on a large population are collected and those who have an incident cancer during the follow-up period are identified. Table 1 divides studies into those that found statistically significant risk reduction with tomato consumption and those that did not. Mean relative risks are presented for each group of studies. This approach increases the importance of small studies compared to large ones, but it is our intention to perceive an overview rather than perform a careful meta-analysis of the published data. Only for prostate cancer patients have small supplementation studies been performed using biomarkers for cancer.

Prostate cancer. The protective association between lycopene and tomato intake and prostate cancer has received significant attention in the past few years. Interestingly, very few case control studies support this association. Only 4 of 13 case control studies found statistically significant negative odds ratios in relation to tomato or lycopene exposure (Table 1). The evidence of an association is strongest in the cohort studies. Giovannucci et al.[12] reported that lycopene intake is related to a lower risk of prostate cancer in U.S. men, with tomato products as the primary sources. Their study involved more than 47,000 male health professionals, 812 of whom developed prostate cancer in the period between 1986 and 1992. All participants in the study completed validated food frequency questionnaires in 1986, 1988, 1990, and 1992. Data clearly

Table 1. Summary of Epidemiologic Studies Examining Tomato or Lycopene Intake or Serum Lycopene Concentrations

Cancer Site	*Reference Number*	*Type of Study*	*Association*	*Number of Studies*	*Mean Relative Risk**
Prostate	12, 58-62, 81-96	Case control	S	4	0.56
			NS	9	0.97
		Cohort	S	4	0.61
			NS	4	1.23
Lung	97-117	Case control	S	6	0.49
			NS	8	0.70
		Cohort	S	0	
			NS	6	0.98
Pancreatic	118-122	Case control	S	3	0.20
			NS	0	
		Cohort	S	2	0.19
			NS	0	
Breast	123-132	Case control	S	2	0.32
			NS	8	0.89
		Cohort	S	1	0.50
			NS	3	0.86
Esophageal/oral cavity, pharynx	133-141	Case control	S	3	0.53
			NS	8	1.01
		Cohort	S	0	
			NS	1	1.70
Stomach	142-156	Case control	S	8	0.47
			NS	7	0.90
		Cohort	S	0	
			NS	1	1.10
Colorectal	157-162	Case control	S	3	0.37
			NS	3	0.96
		Cohort	S	0	
			NS	1	0.36
Skin	163,164	Case control	S	0	
			NS	1	1.17
		Cohort	S	0	
			NS	1	1.67
Ovarian	165	Case control	S	0	
			NS	1	1.36
		Cohort		None	

S = statistically significant risk estimates less than 1.0, NS = not statistically significant.
*Mean of reported relative risk for study regardless of number of study cases.

showed that men with a high consumption of tomato sauce, tomatoes, and pizza had a significantly lower risk of developing prostate cancer. Men who consumed tomato sauce, more than 10 half-cup servings of tomato products per week, had a 35% lower risk of developing prostate cancer compared to men who never ate tomato products. No protective effect was found for vitamin A, β-carotene, lutein, or β-cryptoxanthin or the consumption of fruit and vegetables other than tomatoes. Dietary characteristics and prostate cancer risk were evaluated in a cohort of approximately 14,000 Seventh-Day Adventist households in California. Men were monitored for cancer incidence until the end of 1982.[58] During the 6-year follow-up period, 180 histologically confirmed prostatic cancers were detected among some 78,000 man-years of follow-up. To evaluate the relationship of vitamin A, vitamin C, and β-carotene containing foods to prostate cancer risk, various types of fruits and vegetables commonly found in the Adventist diet were examined. Strong protective relationships were noted with increasing consumption of dried beans, lentils or peas, fresh citrus fruit, raisins, dates and other dried fruits, nuts, and tomatoes. People consuming more than 5 servings of tomatoes per week had a 43% lower risk of prostate cancer compared to men who ate less than 1 serving of tomato product per week. Gann et al.[59] conducted a nested case control study using plasma samples obtained in 1982 from healthy men enrolled in the Physicians' Health Study,[22] a randomized, placebo-controlled trial of aspirin and β-carotene. Gann et al. examined the relationship between plasma concentrations of several major antioxidants and risk of prostate cancer. The subjects included 578 men who developed prostate cancer within 13 years of follow-up and 1294 age and smoking status-matched controls. They quantified α-carotene, β-carotene, β-cryptoxanthin, lutein, and lycopene plus α-tocopherol and γ-tocopherol and retinol. Lycopene was the only antioxidant found at significantly lower mean levels in cases compared to matched controls ($P = .04$ for all cases). Incidence of prostate cancer declined slightly

with increasing plasma lycopene concentration, and there was a stronger inverse association for aggressive prostate cancers.

Two small short-term intervention studies took advantage of the time period between prostate cancer diagnosis and prostatectomy. Kucuk et al.[60] supplemented prostate cancer patients with lycopene (30 mg/day; n = 15) or placebo (n = 11) for 3 weeks prior to their scheduled prostatectomy. Prostatectomy specimens, plasma levels of lycopene, insulin-like growth factor-1, insulin-like growth factor binding protein-3, and prostate-specific antigen (PSA) were measured at baseline and after 3 weeks of supplementation. Seventy-three percent of the patients receiving lycopene but only 18% of the patients in the control group had no involvement of surgical margins and extraprostatic tissues with cancer. Eighty-four percent of the subjects in the lycopene group and 45% in the control group had tumors less than 4 mm in size. Despite the small sample size, these differences were statistically significant. PSA levels decreased by 18% in the intervention group, whereas they increased by 14% in the control group. These differences were not statistically significant and surprisingly, the researchers did not find a significant increase in plasma lycopene concentrations in the intervention group. Our research group[61] supplemented 32 newly diagnosed prostate cancer patients with 200 g of tomato spaghetti sauce baked into pasta entrees (30 mg lycopene/day) for 3 weeks prior to prostatectomy. Prostate lycopene concentrations rose 3-fold, and DNA damage measured as 8-OHdG/dG in leukocytes decreased by 21%. Serum PSA concentrations also decreased by 17% in the men receiving tomato sauce. Oxidative DNA damage in prostate was 28% lower in men consuming the tomato sauce compared to a control group of prostatectomy patients not participating in the study. A histochemical evaluation of 8-OHdG showed that the DNA damage was greatly reduced in prostate cancer cells. Although this study demonstrated that tomatoes have an *in vivo* protective effect against oxidative DNA damage, it is not clear whether a decrease in DNA damage to cancer cells is a positive or negative outcome, if this promotes the greater survival of these cells. We also found increased apoptosis in prostate cancer cells after tomato sauce consumption.

Finally, a case study report described a dramatic decrease in serum PSA concentration in a patient with metastatic prostate cancer in the few months after taking a combination of 10 mg lycopene and 900 mg saw palmetto daily, with a disappearance of clinical evidence of metastatic cancer during an 18-month follow-up.[62]

The cohort studies, considered together with these small clinical trials, point to the need for further phase 2 studies to explore not only the possible preventive action of tomatoes or lycopene, but also possible therapeutic use of either tomatoes or lycopene as an adjunct to conventional treatment.

Other cancer sites. For cancer sites other than prostate, the evidence for a protective effect for tomato product consumption is equivocal. Of the 77 studies that explored the effect of tomato intake associated with various cancer sites, only 28 found statistically significant risk reductions. For example, there were 14 case-control lung cancer studies, with 6 showing a statistically significant risk reduction for cancer incidence, averaging 51%. The 8 remaining studies also tended toward a protective effect of 30% lower risk. However, the cohort studies showed no protective effect of tomato product consumption, raising the possibility that cancer cases in the case control studies had changed dietary habits or had low plasma levels of lycopene due to the disease (Table 1). Surprisingly, the 5 studies (both cohort and case control) evaluating risk reduction of pancreatic cancer and tomato product consumption, showed statistically significant reductions in cancer risk of about 80%. Breast cancer risk was not reduced by tomato consumption. Of the 10 case control studies, only 2 studies showed significant reductions in risk and 3 of 4 cohort studies were negative. Tomato consumption was not associated with protection of esophageal/oral cavity and pharyngeal cancers, with 8 of 11 case control studies showing no risk reduction; the single cohort study was also negative. This is surprising because the one cancer type where β-carotene seems to have a protective effect in clinical trial, is head and neck cancer.[63] Of the 15 case control studies exploring stomach cancer, 8 showed risk reductions averaging 53% and 8 studies showed no effect. Stomach cancer is prevalent in regions with very low tomato product consumption. Therefore, low tomato or lycopene exposure of the population in some of these studies may have obscured any protective effect. Six case control studies have explored the association between tomato product consumption and colorectal cancers. Three studies found statistically significant risk reductions averaging 63%, whereas 3 studies found no association. Skin and ovarian cancers had no risk reduction with high tomato consumption, but there have been very few studies.

The role of tomato product consumption in the prevention of cancers at various sites is still undetermined, but further epidemiological studies are unlikely to add further clarity without greater definition of confounding population variables and better measurement of intake and absorption of the bioactive components of tomatoes.

Food Sources, Bioavailability, and Metabolism of Lycopene

For those who may be interested in increasing lycopene in their diet, some knowledge of tomato consumption and lycopene absorption and metabolism is important.

Sources

Lycopene is narrowly distributed in food and found predominantly in tomato products.[64] Tomatoes and tomato products are also relatively rich sources of β-carotene, vitamin C, folate, and potassium.[65] Relative to other phytonutrients, the most abundant in tomatoes are the carotenoids. Lycopene is the most prominent, followed by phenolic compounds, β-carotene, and lutein, as well as several minor carotenoids including phytoene and phytofluene.[66] The antioxidant activity of lycopene, as well as ascorbate and polyphenols and their abundance in tomatoes, makes these foods rich sources of antioxidant activity.

The content of lycopene in tomatoes differs with tomato varieties. Some of the red varieties such as Flavourtop or Moneymaker contain up to 5 mg/100 g raw fruit, whereas the lycopene content of yellow varieties is only about 0.5 mg/100 g raw fruit.[67] Other sources of lycopene are watermelon, guava, rosehips, and pink grapefruit. However, tomatoes and tomato-based products account for 85% of dietary lycopene in the North American diet.[65] There is little loss of lycopene in tomato products during cooking.[68]

Absorption and Bioavailability

Lycopene is released from food matrices and solubilized in the gut, and its bioavailability depends on various factors such as food processing or coingestion of fat.[69] The efficiency of release is influenced by such factors as disposition of lycopene in the food matrix, particle size after mastication and stomach action, and the efficiency of digestive enzymes.[70] Lycopene is bound to the skin and fiber in fresh tomatoes and is less available in uncooked tomatoes compared to cooked tomatoes. Mild cooking disrupts the cell structure of the tomato, making the lycopene more available. For that reason, the Mediterranean way of consuming cooked tomatoes together with some olive oil favors maximal absorption of this antioxidant. From the research conducted by Gartner et al.,[71] ingestion of tomato paste was found to yield 2.5-fold higher lycopene concentrations compared to ingestion of fresh tomatoes. Thus, in humans, the bioavailability of lycopene is greater from tomato paste than from fresh tomatoes.

Transport

After absorption into the intestinal mucosal cells, lycopene is transported in the plasma exclusively by the lipoprotein system. Chylomicrons are responsible for the transport of lycopene from the intestinal mucosa to the blood stream via the lymphatics. It is thought that hydrocarbons, such as lycopene, exist in the hydrophobic core of the particle. Lycopene is primarily transported in LDLs after chylomicron clearance. Approximately 75% of the hydrocarbons (β-carotene and lycopene) are associated with LDL and the remaining 25% with HDLs and very low density lipoproteins.[70] The distribution of lycopene among lipoproteins is similar to that of β-carotene and similar in men and women.[72,73] Lycopene is a predominant carotenoid in human plasma in the United States. Other major plasma carotenoids include α-carotene, β-carotene, lutein, zeaxanthin, and β-cryptoxanthin.[69] In the United States, lycopene accounts for approximately 40% of the total blood carotenoids compared to less than 10% in Asians.[74] Lycopene is also a major carotenoid in a variety of human tissues,[75,76] indicating that there is effective transfer from plasma lipoproteins to tissues. Lycopene is predominantly found in testes and adrenals, but significant amounts are also found in the liver, adipose tissue, prostate, kidney, and ovary.[75,76] Stahl and Sies[77] found that lycopene uptake varies with individuals and that intake of unheated tomato juice did not increase serum lycopene concentrations. However, the consumption of heated tomato juice increased lycopene concentrations in the serum. The maximum peak serum concentrations were always reached between 24 and 48 hours, and the half-life of lycopene in human serum was between 12 and 31 days.[78] The data showed that there are interindividual differences in lycopene uptake from a dietary source.

Conclusion and Recommendations

Evidence for a protective effect against prostate cancer for lycopene or tomatoes is promising. Although 30% of the case control studies and 50% of the cohort studies showed a protective effect, 2 of the prostate studies were well-designed studies with large sample sizes.[13,22] Both studies showed a more protective effect for advanced prostate cancers and showed a significant dose response. The cell culture studies point to plausible mechanisms of action for lycopene, and the human studies demonstrated that lycopene or other substances can prevent oxidative DNA damage in leukocyte and prostate tissue and may modulate PSA concentrations. Whether these actions of lycopene are important for other cancer sites remains to be determined.

What might be the most appropriate interim advice for clients who have a risk for cancer or have been diagnosed with cancer, especially with prostate cancer? All positive studies have involved the consumption

of tomato products as part of the normal diet, not of lycopene alone. The 2 small prostate cancer trials[60,61] used doses of 30 mg of lycopene/day, but Chen et al.[61] delivered the dose as tomato sauce baked into pasta dishes, where lycopene bioavailability was likely lower compared to lycopene supplements. The study by Giovannucci et al.[13] identified risk reduction when lycopene consumption from foods averaged 6.5 mg/day. Large clinical trials with β-carotene supplements that appeared to increase lung cancer incidences in smokers, who also consumed alcohol, used doses ranging from 20 to 50 mg/day of highly bioavailable β-carotene. The Institute of Medicine Antioxidant Group, which convened in 1999, declined to establish the dietary reference intake (DRI) for any of the carotenoids and also declined to set an upper tolerable limit for any of the carotenoids due to insufficient data. However, it recommended that the use of carotenoid supplements be discouraged in favor of increasing consumption of all fruits and vegetables to more than 5 servings per day.[79]

Taken together, the best advice might be to increase tomato product consumption to provide more than 6 mg of lycopene per day, and if lycopene supplements are preferred, the dose should not exceed 5 mg/day (the amount that could normally be obtained in the diet). The question remains whether smokers and moderate drinkers should avoid lycopene. The β-carotene lung cancer trials, in which the prevalence of smoking and drinking was high, found reduced risk for lung cancer with high β-carotene plasma concentrations in the control group.[13,22] This would argue that the consumption of fruits and vegetables, including tomato products, offers no risk for smokers. However, there is insufficient data to determine whether lycopene supplementation, particularly at high doses, is problematic for smokers and drinkers, and such supplementation should be approached with caution. Likewise, there is some concern in suggesting lycopene supplements, which produce their own oxidative stress, to cancer patients undergoing radiation or chemotherapy. Lycopene can act as a pro-oxidant at high concentrations, and this property may be enhanced under conditions of especially high oxidative stress.[80] The best overall advice is to encourage the consumption of a wide range of fruits and vegetables and to remind patients that tomato sauces and ketchup can be a valuable part of the diet.

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Editor's Note

Eun-Sun Hwang and Phyllis E. Bowen present a thorough review of the literature on tomato products and cancer, from a prevention viewpoint, but with comments directed to cancer patients as well. Although this journal focuses on cancer treatment, we would much rather enjoy a healthy population than treat the unfortunately large numbers of cancer patients we now see, so we plan to publish some prevention articles. The authors' comments about the usefulness of eating tomato products and not relying only on lycopene supplements is good advice for both cancer patients and health professionals. The focus of this review is on prevention rather than therapy, but the authors do address some comments to the therapeutic value of tomato products and lycopene in prostate cancer. Therapeutic value certainly cannot be said to have been proven, but studies such as those of O. Kucuk do drive home the potential value of nutritional interventions with tomato products, and probably with other vegetables as well, in prostate cancer; the efficacy of lycopene supplementation alone is less clear.