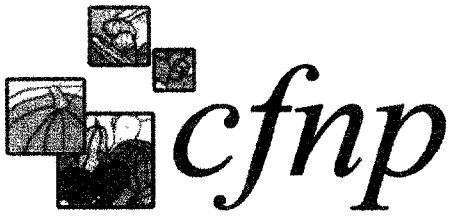

Center for Food and Nutrition Policy
Virginia Tech - Alexandria

The Relationship Between Consumption of Tomato Products, Which Contain Lycopene, and Reduced Risk of Prostate Cancer:

An Evidence-based Review of the Scientific Literature Based on the Food and Drug Administration's Guidance for Qualified Health Claims

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EXECUTIVE SUMMARY

Several epidemiological studies have suggested a relationship between increased fruit and vegetable consumption and reduced risk of many types of cancer.[1] Carotenoids are present in a wide variety of fruits and vegetables and may play a role in cancer prevention, possibly due to their antioxidant activities.[2] Lycopene, one of the most potent antioxidants,[3,4] is commonly found in high concentrations in human prostate tissue, and studies have suggested that tomato lycopene may be associated with a reduced risk of cancer, including prostate cancer.[5,6] Prostate cancer is the second-leading cause of cancer-related death for adult males in the United States.

Researchers have attempted to identify the possible mechanisms involved in the relationship between tomato lycopene supplementation or tomato product consumption and reduced risk of prostate cancer. These potential mechanisms include protection against oxidative damage, enhancement of gap junctional communication (GJC), suppression of tumor growth, and stimulation of the anti-inflammatory response.[7,8,9,10] Tomato lycopene may also contribute to the detoxification of xenobiotic metabolites.[11,12,13] These mechanisms suggest a protective role for tomato lycopene with respect to prostate cancer. If so, increased consumption of tomato products, which contain lycopene, may prove to be beneficial for a significant number of individuals.

CFNP has conducted an independent, third-party, evidence-based literature review of the relationship between consumption of tomato products, which contain lycopene, and prostate cancer risk. CFNP established an evidence-based process for the review and rating of the scientific literature based on U.S. Food and Drug Administration's (FDA) interim guidance for qualified health claims. The procedure applies a rigorous, systematic approach to identify all of the relevant scientific literature, provide consistent quality ratings of scientific articles, fully document the methods and analyses for purposes of replication/review, and summarize the overall strength of the evidence using quantitative and qualitative methods.

A review of the scientific literature examining the relationship between tomato lycopene intake and prostate cancer risk yielded very few randomized, controlled intervention trials. Due to the slowly progressive nature of prostate cancer for the vast majority of the male population, randomized, controlled intervention trials are difficult to perform. Randomized, controlled intervention trials are generally more expensive and time-consuming per participant in relation to other types of studies. Attrition and compliance with strict dietary guidelines are also deterrents to a successful randomized, controlled intervention trial. CFNP's literature search resulted in three studies that examined the relationship between lycopene intake and prostate cancer in men who had already been diagnosed with prostate cancer. Although these three studies are relatively well-designed and demonstrate an inverse relationship between lycopene supplementation and prostate cancer progression, they are limited in that they do not study the relationship between lycopene consumption and prostate cancer prevention.

The literature search yielded five Type 2, or prospective observational cohort, studies. Three of these studies consisted of cohorts of U.S. citizens, while the remaining two studies examined cohorts from the Netherlands. All five of these studies have the benefit of containing more than 10,000 participants. Type 3 studies included both case-control studies and non-randomized intervention trials. The non-randomized intervention trials may include either concurrent or historical controls. The literature search for the relationship between lycopene and prostate cancer yielded far more case-control studies (n = 21) than non-randomized intervention trials

(n = 2). Type 4 studies included cross-sectional studies, analyses of secondary disease endpoints in intervention trials, case series, and studies that could not be matched to any of the other categories. Even though this particular category is given less overall emphasis than the other three categories, it is still important scientifically. More so than the other types of studies, Type 4 studies tend to look at the mechanisms behind an observed relationship. Only one study using human subjects was included in this category. Of the remaining eight studies, three were animal studies, four were *in vitro* studies, and one was a risk analysis.

It is believed that synergistic effects of lycopene with other phytonutrients may enhance lycopene's benefits. Research has demonstrated that the benefits associated with lycopene are enhanced by the presence of other compounds.[14] One animal study demonstrated that lycopene given in "pure" form did not inhibit chemically-induced prostate cancer in rats, whereas consumption of tomato powder containing an equivalent amount of lycopene showed a positive effect.[15] These results suggest that lycopene in isolation does not confer the same level of protective benefits and that tomato products contain compounds in addition to lycopene that can modify carcinogenesis.

The lack of significant results in many of the studies may be explained by small sample sizes, little variability in consumption levels of lycopene in tomato products, dietary assessment inaccuracies due to self-reporting bias and challenges in estimating usual intake, and model specification differences. Lycopene bioavailability differences may also complicate interpretation and comparison of results. The relationship between estimated lycopene intake and serum lycopene is very poor, with correlation coefficients of between 0.1 and 0.35 in different populations.[16]

CFNP addressed the "relevance to disease reduction" ranking measure by conducting a preliminary risk assessment using demographic and diet data from CSFII. Risk factors in the model included age, race/ethnicity, and diet variables for tomato products, other fruit and vegetables, and fat consumption.

Consumer research was conducted to provide information about consumers' awareness, perception, and judgment regarding qualified health claims. The sample was derived from the NFO panel consisting of 750 male and female adults who have eaten processed tomato products (i.e. ketchup, pasta sauce) in the past 6 months. The study sample was nationally representative of adults in the U.S. and included a sample of at least 80 males over the age of 40. The study used three different qualified health claims about a relationship between consumption of tomato lycopene and reduced risk of prostate cancer to test consumer understanding of and reaction to example claims.[1] Interviewers asked if the example health claims would motivate them to change or rethink their eating habits and in what ways.

The results show that 45% of the adult population is aware of lycopene. Among those who are aware of lycopene, 60% believe that it is found in tomatoes and tomato products. Others believed that it is found in vegetables (10%) and/or fruits (11%), while 25% did not know which foods contain lycopene. Among those aware of lycopene, Claim A received significantly fewer positive comments (74% vs. 83% and 84%) than Claim B and Claim C. Further, Claim A received a significantly higher number of negative comments than Claim B. This is mainly driven by a combination of respondents perceiving that the general statement in Claim A is not true and/or that processed foods can not be healthy. Across all three claims, the majority of respondents agreed that they would "incorporate more tomato products into diet" and that "lycopene is not an additive". For all three claims, the majority of respondents believed they would have to eat tomato products 1-2 times/day or 1-2 times/week in order to realize a reduction in risk. The

statement that respondents agreed most with was that lycopene "Will reduce the risk of prostate cancer", whereas only 1% felt that it would "Cure prostate cancer." These results indicate that there is a growing awareness of tomato lycopene and that the majority of people are not misled by the tested qualified health claims.

In the opinion of the Center for Food and Nutrition Policy at Virginia Tech in Alexandria, the body of evidence supports a qualified health claim that consumption of tomato products, which contain lycopene, reduces the risk of prostate cancer. CFNP believes the body of evidence corresponds most closely to the criteria that FDA has established for a Second Level or 'B' claim. The FDA's suggested qualifying language for a 'B' claim is "[a]lthough there is scientific evidence supporting the claim, the evidence is not conclusive."

At this time, the evidence does not meet the standard of significant scientific agreement, so an 'A' claim is not appropriate. To support an 'A' claim, the body of evidence would need to include more definitive clinical trials demonstrating a protective effect for tomato products, which contain lycopene, and more evidence from prospective observational studies. In particular, it would be useful to have additional epidemiological evidence from U.S. prospective observational studies other than the Health Professionals Follow-up Study.

A 'B' level claim is defined by the FDA as a moderate/good level of comfort among qualified scientists that the claimed relationship is scientifically valid. The second level is "promising," but not definitive. High to moderate quality studies of study design Types 1 and 2 and sufficient numbers of individuals would be tested to result in a moderate degree of confidence that results could be extrapolated to the target population. Additionally, studies of similar or different design would generally result in similar findings and the benefit would reasonably be considered to be physiologically meaningful and achievable under intake and use conditions that are appropriate for such conventional human food and dietary supplements that would be the subject of the claim.

Criteria for the third level or 'C' claim include maintaining a low consistency with statements from authoritative bodies or being ranked as "low" in terms of scientific support by qualified scientists. The claim must be based mostly on moderate to low quality studies of study design Type 3, and insufficient numbers of individuals would be tested. Additionally, studies of different design would generally result in similar findings but uncertainties would exist. Uncertainties would also exist as to whether the benefit would be considered physiologically meaningful and achievable under intake and use conditions that are appropriate.

The body of evidence reviewed in this report includes multiple prospective observational studies of high quality that support the proposed claim. Furthermore, there are some randomized clinical trials that provide evidence that is consistent with a reduced risk of prostate cancer, but these Type 1 studies have limitations that are discussed in detail in the full report. The overall body of evidence from all types of studies supports the proposed qualified health claim, and only one study presents any evidence of a possible increased risk of prostate cancer.

Plausible mechanisms of action have been proposed and demonstrated in *in vitro* and animal models. The validity of the prospective observational studies is increased because there is theoretical and empirical evidence to explain the observed relationship found in the epidemiological data.

Increased consumption of tomato products is relevant for reduction of prostate cancer risk among adult males. The evidence suggests that reasonable increases in tomato product consumption could lead to a modest, but meaningful, reduction in the disease burden from prostate cancer.

There is no reason to believe that any harm could result from the proposed qualified health claim. Tomato products are GRAS and there is no evidence of toxicity at any reasonable level of consumption. (Please see Appendix B for suggested intake levels of lycopene in tomato products.)

The proposed health claim is consistent with existing authoritative dietary guidance recommending consumption of five or more servings of fruits and vegetables per day. Consumer research shows that consumers will not be misled by the proposed qualified health claim. The research demonstrates that consumers will understand the proposed qualified health claim and respond by increasing their consumption of tomato products.

Therefore, CFNP believes that the body of evidence on the relationship between tomato products which contain lycopene and risk of prostate cancer supports a 'B' claim based on the criteria established by FDA.

[1]Tested Qualified Health Claims:

A: Consumption of processed tomato products like ketchup, pasta sauce, tomato juice, or tomato soup, as part of a healthy diet, may reduce the risk of prostate cancer.

B: Although evidence is not yet conclusive, studies show that consumption of processed tomato products like ketchup, pasta sauce, tomato juice, or tomato soup, as part of a healthy diet, may reduce the risk of prostate cancer.

C: Growing scientific evidence would suggest that consumption of processed tomato products like ketchup, pasta sauce, tomato juice, or tomato soup, as part of a healthy diet, may reduce the risk of prostate cancer.

I. DEFINITION OF THE SUBSTANCE/DISEASE RELATIONSHIP

a. CHEMICAL PROPERTIES OF LYCOPENE

Carotenoids are natural pigments synthesized by plants and microorganisms that absorb light during photosynthesis and protect cells from photosensitization. Studies have also suggested that many carotenoids serve important roles in human health and disease prevention.[17] There are more than 600 known carotenoids, all of which are antioxidants. The structure of a carotenoid determines the color and photochemical properties of the molecule.[18]

Lycopene is the fat-soluble pigment that gives tomatoes, watermelon, pink grapefruit, and other foods their red color. It is a hydrocarbon carotenoid with 11 conjugated double bonds and 2 non-conjugated carbon-carbon double bonds. Unlike β-carotene, lycopene does not have the β-ionone ring structure so it lacks provitamin A activity. Humans do not synthesize lycopene and must depend entirely on dietary sources.

Lycopene is one of the major carotenoids in the diet of North Americans and Europeans. More than 80% of lycopene intake in the U.S. comes from tomato (*Solanum lycopersicum*) products, although apricots, guava, watermelon, rosehips, and pink grapefruit also contribute to dietary intake. The lycopene content of tomatoes can vary significantly with ripening stage and variety of tomato.[19] On average, tomatoes contain approximately 30 mg lycopene/kg raw tomato, tomato juice contains up to 150 mg lycopene/L, and ketchup contains about 100 mg/kg.[20]

Lycopene accounts for about 50% of the carotenoids found in human serum and is among the major carotenoids present in human milk.[21] Unlike other carotenoids, men and women have similar lycopene serum levels.[22] Lycopene is the principal carotenoid in adrenal glands, testes, liver, and prostate.[23] The predominant form of lycopene in foods is all-*trans* lycopene whereas *cis* forms of lycopene are predominant in human tissue and serum. It is not clear whether the *cis* isomers are preferentially absorbed or whether all-*trans* lycopene is isomerized prior to absorption.[24]

It is also not known whether lycopene affects the bioavailability of other carotenoids. Studies evaluating lycopene from tomatoes as a component of the diet have examined the effects of a complex of tomato phytonutrients acting in coordination. It is believed that synergistic effects of lycopene with other phytonutrients may enhance lycopene's benefits. Research has demonstrated that the benefits associated with lycopene are enhanced by the presence of other compounds.[25]

The bioavailability of lycopene depends on the food matrix and processing. Studies have shown that the bioavailability of lycopene is enhanced in the presence of lipids and thermal processing. The particle size of uncooked food and the presence of dietary fiber also influence the efficacy of carotenoid uptake.[26] Researchers have

suggested that cooking or chopping increases lycopene's bioavailability by breaking down the cell walls, thus making carotenoids more accessible.[27] Porrini et al. showed that plasma lycopene concentrations in subjects who consumed tomato purée were significantly higher than subjects who consumed relative amounts of raw tomatoes.[28] Johnson et al. demonstrated that lycopene ingestion may be enhanced when ingested with β-carotene.[29] Stahl and Sies reported that the estimated serum half-life of lycopene is two to three days. [30]

b. PROSTATE CANCER

The proposed health claim addresses a major health concern in the United States—prostate cancer—and thus meets the criteria set forth in 21 C.F.R. § 101.75. Prostate cancer is the most common visceral malignancy in American men and the second leading cause of cancer-related mortality among U.S. men. According to estimates, there are over 198,000 new cases of prostate cancer, and it is responsible for over 35,000 deaths each year.[31] In 1990, it was estimated that one in every four men in the U.S. will require surgery for either prostate cancer or benign prostatic hyperplasia (BPH) by the time they reach age 80, amounting to medical costs of more than 5 billion dollars each year.[32]

The risk of prostate cancer increases with age, exhibiting one of the steepest age-specific incidence curves observed,[33] and varies with race but not with socioeconomic status. Family history of prostate cancer significantly increases an individual's risk of prostate cancer. The relative risk is increased 2- to 3-fold for men having a first degree relative with prostate cancer compared to those with no family history of prostate cancer.[34] African-American men have an incidence of prostate cancer that is 1.5 times that of white men, while Japanese Americans have the lowest incidence rate.[35] The occurrence of prostatic intraepithelial neoplasia (PIN) and latent prostate cancer does not differ significantly across different geographic regions of the world, even though different geographic areas exhibit significantly different rates of prostate cancer mortality.[36] These observations suggest that environmental factors, including diet and nutrition, play a critical role in the progression from latent to aggressive tumors.[37]

There is considerable interest in evaluating the role of steroid hormones, such as testosterone, in the development of prostate cancer because of their roles in the growth and maintenance of the prostate gland.[38] Other hormones, including prolactin, growth hormone, insulin and insulin-like growth factors, thyroid hormones, adrenal hormones, and estrogen, also affect the prostate gland. It is apparent that hormone profiles and receptor activity influence prostate cancer progression.[39] During its early stages, prostate cancer is sensitive to androgens and may regress when androgen stimulation is withdrawn.[40] Differences in hormone levels may account for racial differences in prostate cancer incidence. However, the relationship between prostate cancer and hormone levels is not well understood and more research is necessary.

Other possible prostate cancer risk factors include smoking, alcohol consumption, dietary fat intake, diet composition, overweight/obesity, and physical activity levels. Several studies have also suggested that there is a positive association between vasectomy and risk of prostate cancer, but many studies have disputed this link.[41,42,43,44] Specific genetic variations may also contribute to individual risk of prostate cancer. Preliminary evidence suggests that these variations may be related to hormone regulation, which may explain differences in racial incidence rates of prostate cancer.[45]

Prostate Cancer Biomarkers

Digital Rectal Examination (DRE) and Prostate-Specific Antigen (PSA) are the primary tools available for diagnosis, staging, and monitoring of prostate cancer.[46] Measurement of serum PSA as a diagnostic tool has resulted in a 20% increase in the detection of clinically localized prostate cancer. However, roughly one-third of new cases are classified as locally advanced at the time of diagnosis.[47] Although serum PSA is not specific to prostate cancer, several studies have shown that PSA level correlates directly with advancing clinical and pathological stage.[48,49] Studies have demonstrated that, in general, PSA is the most sensitive and reliable marker presently available for measuring the progression of prostate cancer and response to therapy.[50]

The most widely used histological grading system in the United States is the Gleason Grading System, which correlates directly with pathological extent of disease.[51] The Gleason score is based on a low-power microscopic description of the histological architecture of the cancer.[52] The score describes how closely the malignant glandular microstructures resemble normal ones, with a lower number being closer to normal and describing a tumor with less potential to spread. [53] By assessing a patient's Gleason score together with the serum PSA level, the physician is able to estimate the stage of prostate cancer progression as well as determine the appropriate treatment method.

Research suggests that insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) play an important role in the regulation of prostate cancer cell growth.[54] Epidemiological studies have found an association between elevated serum IGF-1 levels and increased risk of prostate cancer.[55] Chan et al. found that IGF-1 was significantly associated with prostate cancer risk in a univariate analysis; men in the highest quartile had an RR of 2.4 (95% CI =1.2 to 4.7) compared with men in the lowest quartile. With further adjustment for IGFBP-3, the men in the study sample had more than four times the risk of prostate cancer compared with men in the reference group (RR = 4.3; 95% CI =1.8 to 10.6).[56] Genetic differences in tissue IGF-1 expression may explain the difference in prostate cancer rates between African Americans and Caucasians since this difference is correlated with differences in their respective IGF-1 serum levels.[57]

Wetterau et al. demonstrated that IGF-1 stimulates telomerase activity in prostate cancer cells through a dual mode of action, including early rapid effects involving

phosphorylation of hTERT by AKT1 protein kinase and later up-regulation of hTERT expression.[58] However, the relationship between IGF-1 and prostate cancer is not well understood. Woodson et al. found no evidence to support a causal association between serum IGF-1 or IGFBP-3 and the risk of prostate cancer. It is possible that serum IGF-1 may be serving as a tumor marker rather than an etiologic factor in prostate cancer.[59] Therefore, any study that focused exclusively on the relationship between serum IGF-1 levels and prostate cancer risk was classified as an analysis of a secondary disease endpoint and was included in the Type 4 category.

Together, the Gleason score, serum PSA level, and DRE provide the best available means of identifying prostate tumor stage and aggressiveness. There are still significant gaps in the understanding of prostate cancer progression and its causes. It is likely that the development of prostate cancer in most men takes decades, making identification of prevention strategies critical.

c. Association Between Lycopene and Prostate Cancer

A thorough review of numerous epidemiological studies has shown a relationship between increased fruit and vegetable consumption and reduced risk of many types of cancer.[60] Carotenoids are present in a wide variety of fruits and vegetables and may play a role in cancer prevention, possibly due to their antioxidant activities.[61] Lycopene, a carotenoid considered one of the most potent antioxidants,[62,63] is found in high concentrations in human prostate tissue, and studies have suggested that lycopene may be associated with a reduced risk of cancer, particularly prostate cancer.[64,65] Major dietary sources of lycopene include tomatoes and tomato products.

Animal research has shown that lycopene given in "pure" form does not inhibit chemically-induced prostate cancer in rats. However, consumption of tomato powder containing an equivalent amount of lycopene has shown positive effects.[66] Thus tomato products appear to contain compounds in addition to lycopene that can modify carcinogenesis. Because of a possible relationship between consumption of tomato products, which contain lycopene, and decreased risk of prostate cancer, researchers have attempted to identify mechanisms involved in this relationship.

d. Hypothesized Mechanisms for the Role of Lycopene in Prostate Cancer

Overview

Several mechanisms have been proposed to explain an inverse relationship between the consumption of tomato products, which contain lycopene, and prostate cancer risk. These mechanisms include protection against oxidative damage, enhancement of gap junctional communication (GJC), suppression of tumor growth, and stimulation of the anti-inflammatory response.[67,68,69,70] Lycopene may also contribute to the detoxification of xenobiotic metabolites.[71,72,73] Xenobiotics are chemical compounds that do not naturally occur in living organisms. They are believed to be resistant to environmental degradation.[74] Currently, it is unclear what role, if any, this

potential mechanism of lycopene plays in relation to prostate cancer. Only protection against oxidative damage, enhancement of GJC, suppression of tumor growth, and stimulation of the anti-inflammatory response have shown promise as mechanisms for this relationship.[75]

The potential mechanisms of lycopene in relation to prostate cancer can be categorized into oxidative and non-oxidative processes.[76] Oxidative processes include singlet oxygen quenching and peroxyl radical scavenging. Non-oxidative processes include enhancement of GJC, suppression of tumor growth, stimulation of the anti-inflammatory response, and detoxification of xenobiotic metabolites.

Protection Against Oxidative Damage

The most generally accepted mechanism for explaining the relationship between consumption of tomato products, which contain lycopene, and prostate cancer risk reduction is due to the efficacy of lycopene as an antioxidant.[77,78,79,80] Antioxidants are substances, either synthetic or natural, that prevent or delay the oxidation of other substances. Oxidative stress results in a biological system being forced into a highly activated state due to a loss of control of its regulatory abilities.[81] Prolonged oxidative stress may lead to oxidative damage of cellular DNA, proteins, lipoproteins and/or lipids.[82,83,84] Oxidative damage has been implicated as a possible cause of, or contributor to, many types of cancer, as well as cardiovascular disease, diabetes, osteoporosis, and macular degeneration. Lycopene is twice as effective as β-carotene, and ten times more effective than α-tocopherol, in quenching reactive oxygen species, especially singlet oxygen ($^1O_2$).[85] Singlet oxygen is an energized, but uncharged, form of oxygen that is highly unstable and is the biologically occurring excited state of ground state, or triplet, oxygen ($^3O_2$).

Lycopene is a highly potent antioxidant due to its unique structure of eleven conjugated and two non-conjugated double bonds arranged linearly in the all-*trans* form. The all-*trans* configuration is the most thermodynamically stable form of lycopene. Although lycopene and β-carotene are both carotenoids, lycopene lacks the β-ionone ring structure and can not form vitamin A. Lycopene can undergo *cis-trans* isomerization when exposed to light, thermal energy or chemical reactions.

Singlet oxygen is generated during normal aerobic metabolism. A sensitizer (S) is excited to its first excited state (^1S) and then undergoes an intersystem crossing to its meta-stable triplet state (^3S), resulting in a slight loss of energy.[86] Although ^3S is still an excited form of the sensitizer, it is more stable and longer-lived than ^1S.

$$S \rightarrow {}^1S \rightarrow {}^3S$$

Sensitizers may originate from within (endogenous) or from outside (exogenous) an organism. Endogenous sensitizers include porphyrins, chlorophylls, bilirubin and riboflavin. Exogenous sensitizers include psoralen, anthracene, rose bengal and

methylene blue. Triplet-state sensitizer can initiate a further reaction with $^3O_2$ to form $^1O_2$.

$$^3S + {}^3O_2 \rightarrow S + {}^1O_2$$

The resulting $^1O_2$ can then react with lycopene (L) to form $^3O_2$ and triplet-excited lycopene ($^3L^*$). Lycopene facilitates the conversion of $^1O_2$ to $^3O_2$, which prevents or limits the oxidative damage caused by $^1O_2$.

$$^1O_2 + L \rightarrow {}^3O_2 + {}^3L^*$$

Triplet-excited lycopene transfers its excitation energy through rotational and vibrational interactions with its solvent to return to its ground state.[87]

$$^3L^* \rightarrow L + \text{Thermal Energy}$$

This particular mechanism of lycopene is considered a physical reaction since lycopene remains intact and can undergo further cycles of singlet oxygen quenching. In this reaction, lycopene acts like a catalyst during the quenching of singlet oxygen. Lycopene may also perform chemical quenching of singlet oxygen, but this probably accounts for less than 1% of the overall singlet oxygen quenching contribution of lycopene. Chemical quenching is responsible for the final decomposition, or "bleaching," of lycopene.[88] The decomposition products of lycopene may also possess biological activities.[89]

The scavenging of peroxyl radicals is another potential anti-oxidative function of lycopene in relation to prostate cancer. In order to protect tissues from damage caused by free radicals, lycopene must be able to interrupt the harmful oxidation resulting from free-radical mediated processes, possibly by breaking the free-radical chain reaction.[90] Lycopene is a highly reactive scavenger of peroxyl radicals. This might be due to the easy addition of peroxyl radicals to its long polyene chain, but hydrogen abstractions may also play a role. Because lycopene is a highly reactive scavenger of peroxyl radicals, it is quickly decomposed, or "bleached," and affords less protection against peroxyl radicals than other carotenoids.[91,92]

Enhancement of Gap Junctional Communication (GJC)

Lycopene may be able to influence prostate cancer risk and/or progression through its ability to enhance cellular GJC by stabilizing connexin43 mRNA.[93] Connexin43 is part of a group of homologous proteins that form the intermembrane channels of gap junctions. Gap junctions are cell-to-cell channels that enable connected cells to exchange low-molecular-weight compounds, such as nutrients and signaling molecules. Cancer cells are normally-functioning cells that have been chemically transformed. This transformation compromises the integrity of the gap junction, resulting in a loss of GJC.[94]

The structure of the end-groups influences the effect a particular carotenoid exerts upon cellular GJC. Carotenoids with six-membered rings as end-groups were found to be more effective inducers of GJC than carotenoids with five-membered rings. Even though carotenoids lacking cyclic end-groups typically show no significant effects on GJC, lycopene still seems to have some stimulatory effect on this process.[95] The exact mechanism is unknown, but some studies suggest that the central cleavage products of carotenoids are ultimately the active components triggering GJC.[96,97] The central cleavage analog of lycopene (acyclo-retinoic acid) does not appear to stimulate GJC, but other oxidative products of lycopene may perform this function.[98]

Suppression of Tumor Growth

Insulin-like growth factors (IGFs) play an influential role in the formation and proliferation of tumor cells.[99,100] Insulin-like growth factor-1 (IGF-1) is a peptide that affects the proliferation of both normal and malignant cells,[101] including prostate epithelial cells,[102] through its ability to stimulate mitosis and inhibit apoptosis. IGF-1 is manufactured in the liver as the result of growth hormone stimulation, but circulating levels of IGF-1 are influenced by nutritional status.[103] IGF-1 stimulates tumor formation and progression by influencing the function of IGF-1 receptors in tumor-forming cells,[104,105,106] resulting in tyrosine autophosphorylation of the receptor. This leads to the activation of downstream signaling cascades.[107]

An epidemiological study of participants in the Physicians' Health Study found a strong positive association between IGF-1 levels and prostate cancer risk.[108] Several *in vitro* studies using various cancer cell lines have shown that lycopene does have an inhibitory effect on cancer cell growth. Lycopene treatment of MCF-7 mammary cancer cells significantly reduced the IGF-1 stimulation of tyrosine phosphorylation of insulin receptor substrate 1 and the binding capacity of the AP-1 transcription complex.[109,110] The resulting inhibition of MCF-7 cell growth was not associated with changes in the quantity or affinity of the IGF-1 receptors. Instead, this result was attributed to an increase in membrane-associated IGF-binding proteins followed by a decrease in IGF-1 receptor activation. Lycopene also suppressed IGF-stimulated progression through the G1 and S phases of the cell cycle. The G1 phase of the cell cycle is the gap that follows mitosis. The G1 phase is followed by the synthesis (S) phase, during which DNA is replicated, in preparation for the next cell cycle. Lycopene not only inhibited cancer cell growth and cell cycle progression, but it produced these effects at physiologically attainable levels of up to 3.0 μM. In addition, the inhibitory effects of lycopene on the MCF-7 cell line were not accompanied by apoptotic or necrotic cell death.[111]

Lycopene in combination with 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] exhibited an even greater inhibitory effect on cell growth and cell cycle progression in the HL-60 promyelocytic leukemia cell line than did lycopene alone. The specialization of cell function, or cell differentiation, is reduced or lost in malignant cells. Cell differentiation was further stimulated when HL-60 cells were treated with both lycopene and $1,25(OH)_2D_3$ than with lycopene alone.[112] Although $1,25(OH)_2D_3$ is a

natural anticancer compound, it is therapeutically active only at toxic concentrations when used alone. Combining $1,25(OH)_2D_3$ with lycopene allows $1,25(OH)_2D_3$ to be effective at nontoxic levels in addition to enhancing the therapeutic effect of lycopene. Other studies have suggested that the oxidation products of lycopene, rather than lycopene itself, may be responsible for the inhibition of cell growth in the HL-60 cell line[113] as well as the PC-3 and DU-145 human prostate cancer cell lines[114] by inducing apoptosis.

Stimulation of the Anti-Inflammatory Response

A series of events, known as the inflammatory response, occurs at the vascular and cellular levels when there is injury to bodily tissue. The inflammatory response is characterized by the excretion of enzymes, or cytokines, from the injured cells. These cytokines cause a brief constriction of the surrounding small blood vessels followed by dilation and increased blood flow to the entire injured area. This generates substantial amounts of reactive oxygen species and free radicals, resulting in oxidative stress. Injury from bacteria or viruses and their related toxins, excessive heat or cold, trauma, excessive acids or alkalis, irradiation, and exercise-induced muscle damage are all causes of the inflammatory response.[115]

Lycopene may play a role in the anti-inflammatory response due to its potent anti-oxidant properties. Lycopene's stimulation of the anti-inflammatory response is classified as a non-oxidative process since this potential mechanism is not associated with normal aerobic metabolism. After the acute phase response of inflammation, one study discovered a significant decrease in plasma lycopene concentrations.[116] Another study demonstrated a significant increase in plasma and lymphocyte lycopene concentrations after dietary supplementation with tomato puree in humans. A significant reduction in lymphocyte DNA damage was also observed.[117] These two studies lend support to the role of lycopene in the anti-inflammatory response, but much more research is needed on this potential mechanism.

Summary

Numerous scientific studies have examined the role of lycopene in cardiovascular disease, osteoporosis, neurodegenerative diseases, inflammatory conditions, and various types of cancers.[118,119,120] Many of these studies have even observed inverse relationships between lycopene/tomato product consumption or serum/tissue lycopene levels and some diseases, including prostate cancer. Although a protective role for lycopene in many diseases is possible, the high concentrations of lycopene found in the human prostate hints of a compelling link between lycopene and prostate cancer. Many of the possible mechanisms for lycopene's role in prostate cancer prevention and treatment have been reported in the scientific literature. However, only a few of these mechanisms—protection against oxidative damage, enhancement of GJC, suppression of tumor growth, and stimulation of the anti-inflammatory response—are compelling enough to explain the potential relationship between lycopene and prostate cancer. In addition, current literature and ongoing studies indicate that

additional resources will be directed towards clarifying the mechanistic relationships that affect the development and progression of prostate cancer.

II. C.F.R. PRELIMINARY REQUIREMENTS FOR HEALTH CLAIM PETITIONS

Tomatoes and tomato products are foods; lycopene in tomatoes and tomato products is a component of food. Therefore, tomatoes, tomato products, and lycopene in tomatoes and tomato products meet the definition of a substance[121] as defined in 21 C.F.R. § 101.14(a). The claim meets all 21 CFR 101.14 general health claim requirements, *except* for the requirement that the claim meet the significant scientific agreement standard.

The proposed qualified health claim satisfies the criteria set forth in 21 C.F.R. 101.14(b). Tomatoes and tomato products, which contain lycopene, are associated with prostate cancer risk reduction among an identified U.S. population subgroup, i.e. adult males. Tomatoes, tomato products, and lycopene in tomatoes and tomato products contribute nutritive value in accordance with 101.14(b)(3)(i).Tomatoes, tomato products, and lycopene in tomatoes and tomato products are safe and lawful under the applicable food safety provisions of the Federal Food, Drug and Cosmetic Act.

1. Is there an optimum level of the particular substance to be consumed beyond which no benefit would be expected?

   There is no evidence that establishes an optimum level of lycopene consumption beyond which no benefit would be expected.[122] Studies have demonstrated that absorption of lycopene is dose-dependent but not linear, with greater absorption at lower doses.[123]

2. Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?

   Lycopene-containing foods, including tomatoes and tomato products, have a very long history of use with no indication of significant adverse effects.[124] Several studies have demonstrated that the consumption of tomato products and lycopene is safe and well tolerated. [125,126,127,128] Lycopenemia, a carotenoid-induced skin color alteration is the only reported adverse reaction of the consumption of excessive amounts (up to 2 liters per day) of tomato products.[129,130] Lycopenemia is considered harmless and is readily reversible when lycopene ingestion is stopped. The Physician's Desk Reference (PDR) for Nutritional Supplements does not report any side effects associated with lycopene consumption.[131]

3. Are there certain populations that must receive special consideration?

   According to the PDR for Nutritional Supplements, lycopene is contraindicated for those who are hypersensitive to any component of a lycopene-containing preparation. The PDR for Nutritional Supplements

also advises that pregnant women and nursing mothers should only consume lycopene from food sources and not from dietary supplements.

4. What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

   The PDR for Nutritional Supplements lists the following interactions for lycopene: Concomitant intake of cholestyramine, colestipol, mineral oil, orlistat, olestra, and pectin may reduce the absorption of lycopene. Concomitant intake of medium-chain triglycerides and β-carotene may increase the absorption of lycopene.
   The bioavailability of lycopene in tomatoes and tomato products is enhanced when coingested with lipids and fiber.
   Promoting greater consumption of tomatoes and tomato products, which contain lycopene, is consistent with dietary recommendations of increased fruit and vegetable intake.

III. LITERATURE REVIEW

Methodology/Implementation of Interim Guidelines for Evidence-Based Ranking System

The methodology for identifying relevant studies included developing a set of structured literature searches with the assistance of a librarian at the National Library of Medicine. All studies reported in the English language that examined the association between tomato products and/or lycopene and prostate cancer were considered. Studies were identified in the MEDLINE®/PUBMED(which includes Cancer lit and several other smaller databases), Biological Abstracts, Science Citation Index, and Clinicaltrials.gov (used to identify ongoing clinical trials) databases.

We used the MeSH (Medical Subject Headings) tool to choose the search terms used in this analysis. Exact search criteria for all databases included the words: 'lycopene', 'prostate cancer', 'tomato'. The following combinations of search terms were used consistently and the search was repeated throughout the process to capture newly published information:

a. 'Lycopene' and 'Prostate Cancer'
b. 'Lycopene' and 'Tomato'
c. 'Prostate Cancer' and 'Tomato'
d. 'Lycopene' and 'Tomato' and 'Prostate Cancer'

We conducted an initial screening of the literature to eliminate any articles that were captured by the searches but, after further review, were not relevant. We then acquired the articles, made copies, and conducted an initial review of approximately 20 "core" articles. We developed a preliminary evidence summary table that identified several supporting articles, including articles in the Type 1 category. We

did not find any studies that suggested that lycopene consumption was associated with increased risk of prostate cancer.

We developed evaluation criteria, defined study types, and tested the evaluation criteria for consistency. We implemented the evaluation criteria and included a cross-validation of a sub-sample of the "core" articles. Random spot checks were also performed by the Principle Investigator. Evaluation of study quality and weight of evidence included the following steps:

- Development of criteria and forms to rate the quality of studies. These criteria include the factors explicitly mentioned in the FDA release and were further developed using the resources cited in the FDA's interim guidance. We developed two forms to evaluate the studies, one for clinical studies and one for epidemiological studies. The forms include quantitative (number of subjects, quality of design, and overall strength of findings) and qualitative (notes on design or interpretation issues) evaluations of the studies. (see attached forms)
- Testing of criteria and form for consistent application. Implementation of the criteria with cross-validation for a sub-sample and random spot checks from the Principle Investigator.
- Designing a table showing the number of studies of each type and quality rating. Separate sections of the table show the type/quality matrix for the set of studies supporting the claim with statistically significant results, the set supporting the claim but with results that are not statistically significant, the set of studies showing no effect, and the set of studies contradicting the claim (if any).
- Rating the strength of the total body of evidence on the basis of **quantity**, **consistency**, and **relevance to disease risk reduction** in the general population or target subgroup. Ranking the strength of the evidence for a health claim. Reporting the "rank". The overall ranking was developed and validated by three reviewers. The ranking was reviewed internally and was then presented to a meeting of experts for external feedback
- To address the "relevance to disease reduction" ranking measure, CFNP conducted a preliminary risk assessment using demographic and diet data from the Continuing Survey of Food Intakes by Individuals (CSFII).

IV. REVIEW AND RATING OF EXISTING SCIENTIFIC EVIDENCE

a. REVIEW OF LITERATURE

Type 1 Studies

Overview

A review of the scientific literature examining the relationship between lycopene supplementation or tomato/tomato product consumption and risk of prostate cancer did not yield any randomized, controlled intervention trials. Due to the slowly progressive nature of prostate cancer for the vast majority of the male

population, randomized, controlled intervention trials are difficult to execute. Randomized, controlled intervention trials are generally more expensive and time-consuming per participant in relation to other types of studies. Attrition and compliance with strict dietary interventions are also deterrents to successful randomized, controlled intervention trials. The literature search did result in three studies examining the effects of either lycopene or tomato extract supplementation (please see Appendix C) on subjects with confirmed diagnoses of prostate cancer.

Randomized, Controlled Intervention Trials

Ansari and Gupta[132] identified 54 men with histologically confirmed metastatic prostate cancer. Immediately after orchidectomy, half of the subjects received lycopene supplementation (2 mg twice daily) while the other half did not receive any lycopene supplementation. At baseline, mean serum PSA levels did not differ significantly between the orchidectomy alone group (259.7 ng/mL) and the orchidectomy plus lycopene group (250.7 ng/mL). After six months, mean serum PSA levels improved for both groups, but the orchidectomy plus lycopene group (9.1 ng/mL) showed a more marked improvement than the orchidectomy alone group (26.4 ng/mL). However, this difference was not statistically significant. After two years, the improvement in mean serum PSA levels was more consistent in the orchidectomy plus lycopene group (3.0 ng/mL) than in the orchidectomy alone group (9.0 ng/mL). This difference was statistically significant ($P < 0.001$). In addition, more subjects in the orchidectomy plus lycopene group (78%) than in the orchidectomy alone group (40%) experienced a complete PSA response ($P < 0.05$). A complete PSA response was defined as serum PSA levels returning to < 4 ng/mL. Subjects in the orchidectomy plus lycopene group were also more likely to exhibit a complete bone scan response (return to normal bone scan) than those in the orchidectomy alone group ($P < 0.05$).

In the initial study by Kucuk et al.,[133] the effects of supplementation with a tomato oleoresin extract (please see Appendix C) on plasma PSA and IGF-1 levels in 26 men with newly diagnosed, clinically localized prostate cancer (Stage T1 = 14; Stage T2 = 12) were examined. The treatment group (n = 15) received 15 mg of lycopene twice daily via capsules containing a tomato oleoresin extract for 3 weeks prior to prostatectomy. Since tomato oleoresin extract is a very concentrated form of natural tomatoes, these capsules also contain all the other phytochemicals present in tomatoes. The control group (n = 11) received no supplementation prior to prostatectomy. Serum PSA levels decreased by 18% in the intervention group and increased by 14% in the control group. However, serum IGF-1 levels, a controversial secondary disease end-point for prostate cancer, decreased in both groups. In their follow-up study, Kucuk et al.[134] analyzed tumor size, cancer progression, and type of prostatic intraepithelial neoplasia (PIN) within the same 15 treatment subjects and 11 controls. The treatment group had smaller tumors (80% vs. 45%, less than 4 ml), less involvement of surgical margins and/or extra-prostatic tissues with cancer (73%

vs. 18%, organ-confined disease), and less diffuse involvement of the prostate by high-grade PIN (33% vs. 0%, focal involvement) than the control group. It should be noted that the treatment group in the Kucuk et al. studies contained a higher percentage of subjects with stage T1 prostate cancer (66.7%) than was found in the control group (36.4%), possibly biasing the results.

Summary

Although these three studies are relatively well-designed and demonstrate an inverse relationship between lycopene and tomato extract supplementation and prostate cancer progression, they are of limited value in assessing the relationship between lycopene supplementation or tomato/tomato product consumption and prostate cancer prevention. Furthermore, it is difficult to make a more definitive statement concerning the relationship between lycopene or tomato extract supplementation and prostate cancer progression due to the very small sample sizes analyzed in these studies.

Design Type 1 Studies

Study	Sample Size	Quality	Results†
Ansari, M, and Gupta, N. "A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer." *BJU International* 2003; 92:375-8.	54 Treatment Group: 27 Control Group: 27	∅	**SS**
Kucuk, O, Sarkar, F, Sakr, W, Djuric, Z, Pollak, M, Khachik, F, Li, Y, Banerjee, M, Grignon, D, Bertram, J, Crissman, J, Pontes, E, and Wood, D. "Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy." *Cancer Epidemiology, Biomarkers and Prevention* 2001; 10:861-8.	26 Treatment Group: 15 Control Group: 11	+/∅	**SS**
Kucuk, O, Sarkar, F, Djuric, Z, Sakr, W, Pollak, M, Khachik, F, Banerjee, M, Bertram, J, and Wood, D. "Effects of lycopene supplementation in patients with localized prostate cancer." *Experimental Biology and Medicine* 2002; 227:881-5.	26 Treatment Group: 15 Control Group: 11	+/∅	**SS**

†SS (support, significant)
SN (support, not significant)
N (not support)

Type 2 Studies

Overview

Since prospective observational cohort studies usually track large populations over relatively long periods of time, this type of study may be more useful in discerning a relationship between lycopene supplementation or tomato/tomato product consumption and prostate cancer risk. The literature search yielded five prospective observational cohort studies. Three of these studies consisted of cohorts of U.S. citizens, while the remaining two studies examined cohorts from the Netherlands. All five of these studies began with cohorts of more than 10,000 participants. However, some participants were excluded from their respective cohorts for various reasons as noted below.

United States Cohort Studies

Mills et al.[135] studied the relationship between tomato consumption and prostate cancer risk in a cohort of 14,000 non-Hispanic white Seventh-Day Adventist men living in California from 1976 to 1982. Seventh-Day Adventists are instructed by their church to follow a mainly lacto-ovo-vegetarian diet. They are also encouraged to abstain from all tobacco products, alcoholic beverages, and pork products. Mills et al. discovered that tomato consumption (multivariate RR = 0.60 for $\geq$ 5 times/week versus < 1 time/week; 95% CI = 0.37 to 0.97; P = 0.02) was associated with a significantly decreased risk of prostate cancer. A significant reduction in prostate cancer risk was also observed for lower levels of tomato consumption (multivariate RR = 0.64 for 1-4 times/week versus < 1 time/week; 95% CI = 0.42 to 0.97; P = 0.02). In fact, overall tomato consumption was probably under reported since consumption of tomato products was not assessed in this study. Tomato products, especially those that are heated and consumed with a little oil, have greater amounts of biologically available lycopene than unprocessed tomatoes.[136] Tomato products may also contain other phytochemicals that contribute to prostate cancer risk reduction. The results of this study have a somewhat limited application to the general U.S. male population due to the homogeneity of this particular cohort. However, this homogeneity does inherently control for some of the potential confounders present in heterogeneous cohorts.

In the 1995 Giovannucci et al.[137] study, tomato and tomato product consumption was assessed for 47,894 eligible subjects from the Health Professionals Follow-up Study who were initially free of diagnosed cancer. Between 1986 and 1992, 773 new cases of non-stage A1 prostate cancer were documented. The combined intake of tomatoes, tomato sauce, tomato juice, and pizza accounted for 82% of lycopene intake of the participants. This combined intake was inversely associated with the risk of prostate cancer (multivariate RR = 0.65; 95% CI = 0.44 to 0.95; P = 0.01) for a consumption frequency of more than 10 servings/week versus less than 1.5 servings/week and was also inversely associated with the risk

of advanced (stages C and D) prostate cancer (multivariate RR = 0.47; 95% CI = 0.22 to 1.00; P = 0.03) at the same levels of consumption. In their follow-up study, Giovannucci et al.[138] confirmed their previous findings by including additional data obtained between 1992 and 1998 in their analyses. The additional data increased the total to 2481 documented new cases of non-stage A1 prostate cancer since baseline analysis. Total lycopene intake, calculated from reported tomato and tomato product consumption, was associated with a reduced risk of prostate cancer (P = 0.003). Intake of tomato sauce, the primary source of bioavailable lycopene, was associated with an even greater reduction in prostate cancer risk (P < 0.001) for more than 2 servings/week versus less than 1 serving/month, especially for extraprostatic cancers.

An important trend throughout the two Giovannucci et al. studies is the increasing incidence of organ-confined prostate cancer along with the declining incidence of advanced prostate cancer between 1986 and 1998. This development may be attributable to the growing use of plasma PSA levels as a screening tool for prostate cancer. More prostate cancers are being diagnosed and treated earlier than had been done just ten years ago. Earlier diagnosis and treatment reduces fatalities by preventing prostate cancer from spreading beyond the prostate. Therefore, some of the inverse association between tomato and tomato product consumption and prostate cancer risk may be confounded by earlier detection and treatment of prostate cancer, especially in the follow-up study.

International Cohort Studies

An inverse relationship between tomato or tomato juice consumption and prostate cancer risk was not present in a study examining a cohort from the Netherlands. Although this study by Schuurman et al.[139] did not involve a cohort of U.S. citizens, the Netherlands and the U.S. are both economically developed nations that exhibit relatively high rates of prostate cancer.[140] However, the per capita consumption of tomatoes and tomato products in the U.S. far exceeds that of the Netherlands.[141,142] As part of the Netherlands Cohort Study, 58,279 men were followed for 6.3 years. After excluding participants with prevalent cancer (other than skin cancer) at baseline and excluding participants with incomplete or inconsistent dietary data, 610 men with prostate cancer and 1456 male cohort members were included in the analyses. For vegetables categorized in botanical groups, no associations were found with prostate cancer except for an inverse association with pulses when comparing highest versus lowest quintiles of intake (multivariate RR = 0.71; 95% CI = 0.51 to 0.98; P = 0.01). Unexpected results included the observed positive and significant associations between leek (P < 0.05) and orange (P < 0.05) consumption and prostate cancer risk.

The follow-up Schuurman et al.[143] study examined the same cohort for a relationship between total lycopene intake and prostate cancer risk. Total lycopene intake was calculated with the aid of a newly developed food consumption database. The second study was consistent with the first study in

that no association was found between dietary lycopene and risk of prostate cancer. According to the study authors, misclassification of both fruit and vegetable consumption likely led to an underestimation of the strength of these associations. Since tomato product consumption (other than tomato juice) was not included in the semi-quantitative food-frequency questionnaire, even further underestimation of total lycopene intake is possible. Consumption of other phytochemicals found in tomato products that may work in conjunction with lycopene were probably underestimated as well. Because the carotenoid composition of foods was not available at the time of the initial study, there was no way to validate the food-frequency questionnaire for carotenoids. In addition, since the per capita consumption of tomatoes and tomato products in the Netherlands is relatively low, the range between the highest and lowest levels of tomato and tomato product consumption may be too narrow to provide an adequate analysis of prostate cancer risk.

Abstracts

A promising abstract[144] described a cohort study involving 1575 cancer-free Iowa men. Baseline enrollment consisted of the returned mailing of a completed dietary questionnaire from 1987 to 1990. As of 1995, 101 incident prostate cancer cases have been identified. According to the researchers, high intakes of lycopene were inversely associated with prostate cancer risk ($P = 0.03$). However, we have been unable to locate a more detailed description of the study, and our attempts to contact the authors have been unsuccessful.

Design Type Two Studies

Study	Sample Size	Quality	Results[†]
Cerhan, J, Chiu, B, Putnam, S, Parker, A, Robbins, M, Lynch, C, Cantor, K, Torner, J, and Wallace, R. "A cohort study of diet and prostate cancer risk **(abstract)**." *Cancer Epidemiology, Biomarkers and Prevention* 1998; 7:175.	1575	N/A	**SS**
Giovannucci, E, Ascherio, A, Rimm, E, Stampfer, M, Colditz, G, and Willett, W. "Intake of carotenoids and retinol in relation to risk of prostate cancer." *Journal of the National Cancer Institute* 1995; 87:1767-76.	47,894	+	**SS**
Giovannucci, E, Rimm, E, Liu, Y, Stampfer, M, and Willett, W. "A prospective study of tomato products, lycopene, and prostate cancer risk." *Journal of the National Cancer Institute* 2002; 94:391-8.	47,365	+	**SS**

Mills, P, Beeson, W, Phillips, R, and Fraser, G. "Cohort study of diet, lifestyle, and prostate cancer in Adventist men." *Cancer* 1989; 64:598-604	14,000	+	**SS**
Schuurman, A, Goldbohm, R, Dorant, E, and van den Brandt, P. "Vegetable and fruit consumption and prostate cancer risk: a cohort study in the Netherlands." *Cancer Epidemiology, Biomarkers and Prevention* 1998; 7:673-80.	58,279	+/∅	**N**
Schuurman, A, Goldbohm, R, Brants, H, and van den Brandt, P. "A prospective cohort study on intake of retinol, vitamins C and E, and carotenoids and prostate cancer risk (Netherlands)." *Cancer Causes and Control* 2002; 13:573-82.	58,279	+/∅	**N**

†SS (support, significant)
SN (support, not significant)
N (not support)

Type 3 Studies

Overview

Type 3 studies include both case-control studies and non-randomized intervention trials. The non-randomized intervention trials may include either concurrent or historical controls. Since study participants are not randomly assigned to either the intervention or the control group, a much greater potential for bias exists within non-randomized intervention trials than within randomized, controlled intervention trials. For this reason, non-randomized intervention trials are not as rigorous as randomized, controlled intervention trials. Case-control studies are relatively less expensive and time-consuming than other types of studies. Case-control studies also tend to avoid the attrition problems suffered by other study types, but they are more susceptible to bias than other types of studies, especially recall bias. Because of their inherent susceptibility to bias, case-control studies are more likely to suggest erroneous cause and effect relationships.

The literature search for peer-reviewed articles examining the relationship between lycopene supplementation or tomato/tomato product consumption and prostate cancer risk yielded far more case-control studies (n = 21) than non-randomized intervention trials (n = 2). The twenty-one case-control studies include a subset of five nested, case-control studies. These five studies are more rigorous than the other sixteen case-control studies since the cases and controls from the nested, case-control studies originate from either a prospective

observational cohort study or a randomized, controlled intervention trial. Baseline information and/or samples were obtained either as part of, or in addition to, the original study design. Then study participants were monitored for a specified period of time. Subjects that developed prostate cancer, or cases, were identified and matched with disease-free controls from the original study cohort. The five nested, case-control studies may still be susceptible to an intrinsic amount of bias, but their prospective nature should mitigate some of this bias.

Non-Randomized Intervention Trials

As part of an ongoing randomized placebo-controlled study to evaluate the effect of lycopene supplementation on DNA damage in men with prostate cancer, Chen et al.[145] examined the effect of a whole-food intervention on a separate group of prostate cancer patients. Prior to radical prostatectomy, 32 men consumed one of four different prepared tomato sauce-based pasta dishes per day for a period of 3 weeks. Each prepared tomato sauce-based pasta dish contained the equivalent of 30 mg of lycopene. Serum and prostate lycopene concentrations, serum PSA levels, and leukocyte DNA oxidative damage were assessed both prior to and after the whole-food intervention. DNA oxidative damage was defined as the ratio of 8-hydroxy-2'-deoxyguanosine to 2'-deoxyguanosine (8OHdG/dG). In these analyses, the patients served as their own controls. After the whole-food intervention, both serum ($P < 0.001$) and prostate ($P < 0.001$) lycopene concentrations were significantly increased. Leukocyte 8OHdG/dG ($P = 0.005$) and serum PSA levels ($P < 0.001$) were significantly reduced after the whole-food intervention. The relationship between the whole-food intervention and prostate tissue 8OHdG/dG was also examined. Resected prostate tissue was provided by the study subjects after the whole-food intervention, but the control samples were obtained from seven randomly selected prostate cancer patients not involved in this study. Prostate tissue 8OHdG/dG ($P = 0.03$) was also significantly lower in men who had the whole-food intervention than in the randomly selected prostate cancer patients.

In the follow-up study by Bowen et al.[146], this identical study population was used to further examine the relationship between the whole-food intervention and serum and prostate lycopene concentrations, serum PSA levels, and leukocyte and prostate tissue 8OHdG/dG. In addition, nuclear characteristics of the cancer cells were compared between pre-intervention prostate tissue biopsies and post-intervention resected prostate tissue samples. After intervention, serum and prostate lycopene concentrations increased 1.97- and 2.92-fold, respectively; mean serum PSA concentrations decreased by 17.5%; leukocyte 8OHdG/dG decreased by 21.3%; prostate tissue 8OHdG/dG decreased by 28.3%. The post-intervention cancer cells were reduced by 40.5% in mean nuclear density ($P < 0.005$) and by 36.4% in mean area ($P < 0.018$) compared with the pre-intervention cancer cells. Both of these non-randomized intervention trials analyzed the same small sample of men who had already been diagnosed with prostate cancer. Therefore, the relationship between tomato sauce consumption

and prostate cancer risk can not be evaluated directly. However, these two studies did confirm that lycopene concentration is greatly increased in prostate tissue after regular and sustained consumption of foods containing tomato sauce, which is an excellent source of lycopene and other tomato phytochemicals. When this information is combined with the observed decrease in serum PSA concentrations and the decrease in prostate tissue 8OHdG/dG, an inverse relationship between tomato sauce consumption and prostate cancer risk is indirectly supported.

Nested, Case-Control Studies

Hsing et al.[147] examined the relationship between serum lycopene levels and risk of prostate cancer in a cohort of Washington County, MD residents who donated blood for future cancer research in 1974. Hsing et al. found reductions in prostate cancer risk of 19%, 45%, and 50% in the second, third, and fourth quartiles, respectively, compared with the lowest quartile of serum lycopene levels. However, these results were not statistically significant. Gann et al.[148] studied the relationship between prostate cancer risk and plasma lycopene concentration in a cohort (Physicians' Health Study) of healthy men who had contributed blood samples in 1982. According to the study authors, the odds ratios for all prostate cancers declined slightly with increasing quintiles of plasma lycopene concentration, but a significant inverse relationship was only seen between increasing quintiles of plasma lycopene concentration and aggressive prostate cancers ($P = 0.05$).

Huang et al.[149] examined two cohorts of Washington County, MD residents for an association between serum lycopene levels and risk of prostate cancer. Blood samples were provided in 1974 and 1989 from the first (CLUE I) and the second (CLUE II) cohorts, respectively. Huang et al. found no association between prostate cancer risk and serum lycopene levels for either CLUE I or CLUE II. Goodman et al.[150] analyzed the relationship between serum lycopene levels and risk of prostate cancer in a cohort (CARET) of high-risk men recruited from six study centers throughout the U.S. This particular cohort was composed entirely of either asbestos-exposed workers or current/previous heavy smokers. Goodman et al. did not find any association between serum lycopene levels and prostate cancer risk. The relevance of this study to the entire U.S. male population is unclear since only high-risk males were examined.

Nomura et al.[151] did not find any relationship between serum lycopene concentration and prostate cancer risk in a cohort of Japanese Americans residing in Hawaii. Baseline blood samples were collected from this cohort between 1971 and 1975. However, the results from this study may be confounded by the relatively low consumption of tomatoes and tomato products among Asian Americans. The incidence of prostate cancer also tends to be much lower in Asian-American men than in men from other race/ethnic subgroups in the U.S. It is unfortunate that none of these five nested, case-control studies directly examined the relationship between lycopene supplementation or tomato/tomato

product consumption and prostate cancer risk. Only the relationship between serum lycopene levels and prostate cancer risk was analyzed.

Other Case-Control Studies

Although African-American men in the U.S. are 70% more likely than whites to be diagnosed with prostate cancer,[152] studies examining the relationship between lycopene supplementation or tomato/tomato product consumption and prostate cancer risk within this particular population subgroup are difficult to find within the scientific literature. CFNP's literature search was able to identify four case-control studies that attempt to address this relationship.[153,154,155,156] Hayes et al. conducted a population-based case-control study consisting of blacks and whites from three geographic regions (Georgia, Michigan, and New Jersey) within the U.S. The study authors analyzed the relationship between prostate cancer risk and consumption of lycopene-rich foods (raw tomatoes, cooked tomatoes/tomato sauces, tomato juice, and watermelon). Only the combined raw tomato consumption of blacks and whites exhibited a significant inverse association with prostate cancer risk ($P = 0.04$). The data in Table 8 also reveal a significant and positive relationship between tomato juice consumption among whites and risk of prostate cancer ($P = 0.02$). However, this unexpected association is not addressed by the study authors and is not corroborated anywhere in the scientific literature. In a follow-up study involving a subset of this population-based case-control study, Vogt et al. analyzed the relationship between serum lycopene levels and risk of prostate cancer for black and white American males. Vogt et al. found an inverse, though not significant, relationship between prostate cancer risk and the pooled serum lycopene levels of blacks and whites. Furthermore, this study discovered a significant inverse relationship between pooled serum lycopene levels and the risk of aggressive prostate cancer (OR = 0.37 for highest versus lowest quartiles; 95% CI = 0.15 to 0.94; $P = 0.04$). However, no associations were found between prostate cancer risk and serum lycopene levels when black and white men were analyzed separately, possibly due to the resulting smaller sample sizes after disaggregating the combined sample of blacks and whites.

Both Whittemore et al. and Kolonel et al. analyzed the same African-American, white, Japanese, and Chinese participants from another population-based case-control study. These participants were recruited from five geographic regions within the U.S. (Hawaii, San Francisco, and Los Angeles) and Canada (Vancouver and Toronto). Whittemore et al. found no clear or consistent associations between intakes of vitamin A, carotenes or carotenoid-rich foods and risk of prostate cancer. Unfortunately, this study provided no further information on which specific carotenes or carotenoid-rich foods were analyzed. Kolonel et al. found no relationship between tomato or cooked tomato consumption and overall risk of prostate cancer. In addition, consumption of cooked tomatoes was not associated with prostate cancer risk among African-American, white, Japanese, or Chinese men.

Among the twelve remaining case-control studies, four studies examined subjects living in the U.S., while the other eight studies examined subjects living in other countries. Lu et al.[157] conducted a hospital-based case-control study at the Memorial Sloan-Kettering Cancer Center in New York, NY. They discovered a significant inverse relationship between plasma lycopene concentration and prostate cancer risk (OR = 0.17 for highest versus lowest quartile of plasma lycopene concentration; 95% CI = 0.04 to 0.78; P = 0.0052). Le Marchand et al.[158] found no association between tomato consumption and prostate cancer risk in a multi-ethnic (Caucasian, Japanese, Chinese, Filipino, and Hawaiian) cohort residing in Oahu, HI between 1977 and 1983. This study did not include any analysis of the relationship between consumption of processed/cooked tomato products and the risk of prostate cancer. Cohen et al.[159] found a 27% reduced risk of prostate cancer with the consumption of at least three servings per week of cooked tomatoes in a cohort of King County, WA residents, but this association was not statistically significant. After controlling for total vegetable intake, the prostate cancer risk reduction was further decreased to 10%. A study by van Gils et al.[160] examined the relationship between dietary lycopene intake and prostate cancer risk in a cohort residing in the Piedmont Triad area of North Carolina from February 1994 through January 1996. Dietary lycopene intake was estimated from participants' food frequency questionnaires. The study authors discovered that the risk of prostate cancer was highest among men with low intakes of dietary lycopene and who were homogenous for the common allele (Arg/Arg) at codon 399 in the XRCC1 gene. However, this relationship was not statistically significant.

The studies from outside the U.S. include three from Canada, one from Great Britain, two from New Zealand, one from Greece, and one from Uruguay. With the exception of Uruguay, all of these countries are highly economically developed. Uruguay is only slightly less economically developed than the other countries referenced above.[161] All of these countries, including Uruguay, exhibit a considerable incidence of prostate cancer. However, the rate of prostate cancer in Greece, located in Southern Europe, is only about one-fifth the rate of North America (United States and Canada) and about one-half the rate of Western Europe (Great Britain) and Australia/New Zealand.[162] This disparity may be related to the Southern Europeans' consumption of the so-called "Mediterranean diet." The Mediterranean diet is characterized by the consumption of mostly pasta, bread, beans, vegetables (including large quantities of tomatoes and tomato products), fruit, and olive oil.

Tzonou et al.[163] found a significant inverse relationship between cooked tomato consumption and prostate cancer risk (P = 0.003) among Greek men residing in the Greater Athens area. They also reported that increasing consumption of cooked tomatoes from twice a week to four times per week predicts about a 15% reduction in prostate cancer risk. Deneo-Pellegrini et al.[164] did not find any association between lycopene intake and prostate cancer risk in a cohort of Uruguayan men admitted to four major hospitals in Montevideo between 1994

and 1997. Lycopene intake was calculated with the assistance of a carotenoid database developed by the USDA. However, the study authors did observe a significant and inverse association between vegetable intake (P = 0.02) and vegetable and fruit intake combined (P = 0.04) and risk of prostate cancer.

Norrish et al.[165] examined dietary patterns associated with consumption of vegetable oils high in monounsaturated fatty acids (MUFA) in a cohort residing in the greater metropolitan area of Auckland, New Zealand. They reported that diets high in MUFA-rich vegetable oils (> 5.5 ml/day) tended to be high in tomato-based foods (61.92 g/day) among study controls (P = 0.03). Consumption of MUFA-rich vegetable oils (> 5.5 ml/day versus 0 ml/day) was also inversely associated with prostate cancer risk (multivariate RR = 0.5; 95% CI = 0.3 to 0.9; P = 0.005). The follow-up study by Norrish et al.[166] further investigated the relationship between prostate cancer risk and aggregate tomato consumption (raw tomatoes, cooked tomatoes, tomato juice, tomato soup, tomato sauce, and tomato-based pasta dishes) within the same New Zealand cohort. In this study, aggregate tomato consumption was only weakly associated with a reduced risk of prostate cancer. Key et al.[167] did not find any associations between risk of prostate cancer and consumption of raw or cooked tomatoes in a cohort of British men residing in Oxfordshire, West Berkshire, and Leeds.

Rao et al.[168] observed that prostate cancer patients (n = 12) had significantly lower serum (P < 0.004) and prostate tissue (P < 0.05) lycopene levels than their controls (n = 12). No differences in consumption of tomato-based products were observed between cases and controls. In addition to the very small sample size analyzed in this case-control study, the control subjects consisted of five men with untreated muscle invasive bladder cancer and seven men with benign prostatic hyperplasia (BPH). These medical conditions could potentially cause some bias in the study results. Jain et al.[169] examined the effect of total lycopene intake and overall tomato consumption on the risk of prostate cancer in male residents of three Canadian provinces (Ontario, Quebec, and British Columbia). Total lycopene intake was estimated using a carotenoid food composition database obtained from the USDA-National Cancer Institute. The study authors found no association between total lycopene intake and prostate cancer risk. However, overall tomato consumption (tomatoes and tomato soups and sauces) was associated with a significant reduction in prostate cancer risk (multivariate OR = 0.64 for < 9.3 g/day versus > 109.6 g/day; 95% CI = 0.45 to 0.91; P = 0.04). Villeneuve et al.[170] found no association between the combined intake of tomatoes and tomato juice and prostate cancer risk in a cohort of Canadian men residing in the provinces of Prince Edward Island, Nova Scotia, Ontario, Newfoundland, Alberta, Manitoba, Saskatchewan, and British Columbia. This study is highly unusual in that, according to one table in the published paper, the authors found positive and significant associations between the risk of prostate cancer and fruit and fruit juice consumption (P = 0.03) and cereal and grain consumption (P = 0.03).

Design Type Three Studies

Study	Sample Size	Quality	Results[†]
Bowen, P, Chen, L, Stacewicz-Sapuntzakis, M, Duncan, C, Sharifi, R, Ghosh, L, Kim, H, Christov-Tzelkov, K, and van Breemen, R. "Tomato sauce supplementation and prostate cancer: lycopene accumulation and modulation of biomarkers of carcinogenesis." *Experimental Biology and Medicine (Maywood)* 2002; 227:886-93.	32	∅	**SS**
Chen, L, Stacewicz-Sapuntzakis, M, Duncan, C, Sharifi, R, Ghosh, L, van Breemen, R, Ashton, D, and Bowen, P. "Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention." *Journal of the National Cancer Institute* 2001; 93:1872-9.	32	+/∅	**SS**
Cohen, J, Kristal, A, and Stanford, J. "Fruit and vegetable intakes and prostate cancer risk." *Journal of the National Cancer Institute* 2000; 92:61-8.	1230 Cases: 628 Controls: 602	+/∅	**N**
Deneo-Pellegrini, H, De Stefani, E, Ronco, A, and Mendilaharsu, M. "Foods, nutrients and prostate cancer: a case-control study in Uruguay." *British Journal of Cancer* 1999; 80:591-7.	408 Cases: 175 Controls: 233	+/∅	**N**
Gann, P, Ma, J, Giovannucci, E, Willett, W, Sacks, F, Hennekens, C, and Stampfer, M. "Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis." *Cancer Research* 1999; 59:1225-30.	1872 Cases: 578 Controls: 1294	+	**SS** (for aggressive cancers only)
Goodman, G, Schaffer, S, Omenn, G, Chen, C, and King, I. "The association between lung and prostate cancer risk, and serum micronutrients: results and lessons learned from β-carotene and retinol efficacy trial." *Cancer Epidemiology, Biomarkers and Prevention* 2003; 12:518-26.	410 Cases: 205 Controls: 205	+/∅	**N**

Hayes, R, Ziegler, R, Gridley, G, Swanson, C, Greenberg, R, Swanson, G, Schoenberg, J, Silverman, D, Brown, L, Pottern, L, Liff, J, Schwartz, A, Fraumeni, J, and Hoover, R. "Dietary factors and risks for prostate cancer among blacks and whites in the United States." *Cancer Epidemiology, Biomarkers and Prevention* 1999; 8:25-34.	2133 Cases: 932 Controls: 1201	∅	**N/A***
Hsing, A, Comstock, G, Abbey, H, and Polk, B. "Serologic precursors of cancer. Retinol, carotenoids and tocopherol and risk of prostate cancer." *Journal of the National Cancer Institute* 1990; 82:941-6.	206 Cases: 103 Controls: 103	+/∅	**SN**
Huang, H, Alberg, A, Norkus, E, Hoffman, S, Comstock, G, and Helzlsouer, K. "Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer." *American Journal of Epidemiology* 2003; 157:335-44.	CLUE I: 546 Cases: 182 Controls: 364 CLUE II: 426 Cases: 142 Controls: 284	+	**N**
Jain, M, Hislop, G, Howe, G, and Ghadirian, P. "Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada." *Nutrition and Cancer* 1999; 34:173-84.	1253 Cases: 617 Controls: 636	+	**SS** (for overall tomato consumption only)
Key, T, Silcocks, P, Davey, G, Appleby, P, and Bishop, D. "A case-control study of diet and prostate cancer." *British Journal of Cancer* 1997; 76:678-87.	656 Cases: 328 Controls: 328	∅	**N**
Kolonel, L, Hankin, J, Whittemore, A, Wu, A, Gallagher, R, Wilkens, L, John, E, Howe, G, Dreon, D, West, D, and Paffenbarger, R. "Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study." *Cancer Epidemiology, Biomarkers and Prevention* 2000; 9:795-804.	3237 Cases: 1619 Controls: 1618	+	**N**

Le Marchand, L, Hankin, J, Kolonel, L, and Wilkens, L. "Vegetable and fruit consumption in relation to prostate cancer risk in Hawaii: a reevaluation of the effect of dietary beta-carotene." *American Journal of Epidemiology* 1991; 133:215-9.	1351 Cases: 452 Controls: 899	∅	**N**
Lu, Q, Hung, J, Heber, D, Go, V, Reuter, V, Cordon-Cardo, C, Scher, H, Marshall, J, and Zhang, Z. "Inverse associations between plasma lycopene and other carotenoids and prostate cancer." *Cancer Epidemiology, Biomarkers and Prevention* 2001; 10:749-56.	197 Cases: 65 Controls: 132	∅	**SS**
Nomura, A, Stemmermann, G, Lee, J, and Craft, N. "Serum micronutrients and prostate cancer in Japanese Americans in Hawaii." *Cancer Epidemiology, Biomarkers and Prevention* 1997; 6:487-91.	284 Cases: 142 Controls: 142	∅	**N**
Norrish, A, Jackson, R, Sharpe, S, and Skeaff, C. "Men who consume vegetable oils rich in monounsaturated fat: their dietary patterns and risk of prostate cancer (New Zealand)." *Cancer Causes and Control* 2000; 11:609-15.	797 Cases: 317 Controls: 480	+/∅	**SN**
Norrish, A, Jackson, R, Sharpe, S, and Skeaff, C. "Prostate cancer and dietary carotenoids." *American Journal of Epidemiology* 2000; 151:119-23.	797 Cases: 317 Controls: 480	+/∅	**SN**
Rao, A, Fleshner, N, and Agarwal, S. "Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: a case-control study." *Nutrition and Cancer* 1999; 33:159-64.	24 Cases: 12 Controls: 12	+/∅	**SS**
Tzonou, A, Signorello, L, Lagiou, P, Wuu, J, Trichopoulos, D, and Trichopoulou, A. "Diet and cancer of the prostate: a case-control study in Greece." *International Joutnal of Cancer* 1999; 80:704-8.	566 Cases: 320 Controls: 246	+/∅	**SS**

van Gils, C, Bostick, R, Stern, M, and Taylor, J. "Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: an example of polymorphisms in the XRCC1 gene." *Cancer Epidemiology, Biomarkers and Prevention* 2002; 11:1279-84.	260 Cases: 77 Controls: 183	+	**N**
Villeneuve, P, Johnson, K, Kreiger, N, Mao, Y, and the Canadian Cancer Registries Epidemiology Research Group. "Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System." *Cancer Causes and Control* 1999; 10:355-67.	3246 Cases: 1623 Controls: 1623	+/Ø	**N**
Vogt, T, Mayne, S, Graubard, B, Swanson, C, Sowell, A, Schoenberg, J, Swanson, G, Greenberg, R, Hoover, R, Hayes, R, and Ziegler, R. "Serum lycopene, other serum carotenoids, and risk of prostate cancer in US blacks and whites." *American Journal of Epidemiology* 2002; 155:1023-32.	437 Cases: 209 Controls: 228	+/Ø	**SS** (aggressive cancers only)
Whittemore, A, Kolonel, L, Wu, A, John, E, Gallagher, R, Howe, G, Burch, J, Hankin, J, Dreon, D, West, D, Teh, C, and Paffenbarger, R. "Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada." *Journal of the National Cancer Institute* 1995; 87:652-61.	3300 Cases: 1655 Controls: 1645	+/Ø	**N**

†SS (support, significant)
SN (support, not significant)
N (not support)

*This study showed conflicting results concerning tomato and tomato product consumption on the risk of prostate cancer within Table 8. These conflicting results were also not addressed by the study authors. Therefore, this study was classified as N/A in all 'Results' sections within this review.

Type 4 Studies

Overview

Type 4 studies include cross-sectional studies, analyses of secondary disease endpoints in intervention trials, case series, and studies that can not be matched to any of the other categories. Even though Type 4 studies are given less emphasis than the other three types of studies, Type 4 studies are still scientifically relevant. Many Type 4 studies endeavor to identify the mechanism or mechanisms behind observed relationships. Studies attempting to ascertain these mechanisms are critical for establishing cause-effect relationships. Heavy reliance on correlational data is risky since correlation studies can not prove causation on their own. Only until plausible mechanisms for cause-effect relationships have been suggested do these relationships begin to make scientific sense. Hopefully, this leads to a reduction of squandered scientific, as well as political, resources based solely upon spurious correlations.

The only study involving human subjects in this category was the analysis of a secondary disease endpoint. Of the remaining eight studies, three were animal studies, four were *in vitro* studies, and one was a risk analysis of a previous case-control study.

Analysis of Secondary Disease Endpoint

Because of a possible link between lycopene supplementation or tomato/tomato product consumption and prostate cancer risk and a possible link between serum insulin-like growth factor-1 (IGF-1) levels and prostate cancer risk, Mucci et al.[171] studied the relationship between cooked tomato consumption and serum IGF-1 levels. No scientific consensus has yet been reached regarding the role of serum IGF-1 levels in prostate cancer.[172,173,174,175,176,177] Mucci et al. reported that the consumption of cooked tomatoes was significantly and inversely associated with serum IGF-1 levels ($P = 0.014$) in a cohort of cancer-free men recruited from three teaching hospitals in Athens, Greece. How this study contributes to the overall scientific evidence examining the relationship between cooked tomato consumption and prostate cancer risk remains to be seen.

Animal Studies

Guttenplan et al.[178] studied the effects of lycopene-rich tomato oleoresin (LTO) supplementation on prostate mutagenesis in *lacZ* mice. In addition to lycopene, the LTO contained β-carotene, phytofluene, z-carotene, and 2,6-cyclolycopene-1,5-diol. Guttenplan et al. reported a slight, but non-significant, inhibition of both spontaneous (long-term) and benzo[*a*]pyrene-induced (short-term) prostate mutagenesis with LTO supplementation. Boileau et al.[179] analyzed the relationship between prostate cancer risk and lycopene beadlet or whole tomato powder supplementation in male Wistar-Unilever rats. Diets supplemented with

lycopene beadlets contained approximately 161 mg lycopene/kg diet, while diets supplemented with whole tomato powder contained approximately 13 mg lycopene/kg diet. Diets supplemented with whole tomato powder also contained other caroteniods typically found in tomatoes, such as all-*trans* β-carotene, 9-*cis* β-carotene, and other unidentified polar carotenoids. Prostate carcinoma was induced via treatment with testosterone propionate (TP) and *N*-methyl-*N*-nitrosourea (NMU). Rats fed diets supplemented with whole tomato powder had a lower risk of death from prostate cancer than did rats fed diets supplemented with control beadlets (Hazard Ratio = 0.74; 95% CI = 0.59 to 0.93; P = 0.009). However, rats fed diets supplemented with either lycopene beadlets or control beadlets experienced similar prostate cancer-specific mortality rates. The results of this study demonstrated that lycopene given in "pure" form did not inhibit chemically-induced prostate cancer in rats, whereas consumption of tomato powder containing an equivalent amount of lycopene showed a positive effect.[180] These results strongly suggest that tomato products contain compounds in addition to lycopene that can modify carcinogenesis.

Imaida et al.[181] was actually a series of three studies examining the effects of lycopene (99.9%) supplementation on 3,2'-dimethyl-4-aminobiphenol (DMAB)- and 2-amino-1-methylimidazo[4,5-*b*]pyridine (PhIP)-induced prostate carcinogenesis in male F344 rats. The first study discovered a significant reduction ($P < 0.05$) in the incidence of prostate intraepithelial neoplasia (PIN) in the ventral prostate of rats supplemented with lycopene (15 ppm) after termination of DMAB treatment and until the end of the experiment. Lycopene supplementation (15 ppm) concomitant with DMAB treatment was associated with a reduction of PIN in the ventral prostate, but this association was not significant. The second study found a slight, but non-significant, suppression of ventral prostate carcinomas in rats supplemented with lycopene (45 ppm) after termination of DMAB treatment and until the end of the experiment. Supplementation with lower lycopene concentrations (5 ppm and 15ppm) was not associated with suppression of DMAB-induced ventral prostate carcinomas. In the third study, rats were supplemented with lycopene (15 ppm) or lycopene plus curcumin (15 ppm and 500 ppm, respectively) after termination of PhIP treatment and until the end of the study. No associations were seen between lycopene supplementation alone or lycopene plus curcumin supplementation and PhIP-induced PIN or carcinomas in the ventral prostate.

Cell Culture Studies

Richards et al.[182] observed a significant decrease in cell count in the LNCaP human prostate cancer cell line when incubated with 10 μM of lycopene ($P < 0.05$) for 24 hours when compared to the control culture. No significant decrease in cell count was observed in the LNCaP cell line when incubated for 24 hours with only 1 μM of lycopene. In addition, no further cell count reductions were detected with either 1 μM or 10 μM of lycopene after 48 and 72 hours of incubation. Total protein levels in the LNCaP cell line significantly decreased

after 48 and 72 hours of incubation in both lycopene treatment groups ($P < 0.05$) when compared to their respective controls. Kim et al.[183] studied the effects of various lycopene dilutions on LNCaP cell proliferation. The lycopene dilutions were prepared from a micro-emulsion containing 0.258% lycopene in an appropriate vehicle. Lycopene concentrations of 10^{-6} and 10^{-5} M significantly inhibited LNCaP cell proliferation after incubation for 24, 48, 72, and 96 hours compared with controls at the same dilutions ($P < 0.05$) although lycopene at 10^{-4} M completely inhibited cell proliferation at all incubation periods. Lycopene concentrations of 10^{-9}, 10^{-8}, and 10^{-7} M significantly inhibited LNCaP cell proliferation after incubation for 24, 48, 72, and 96 hours in a dose-dependent manner compared with controls at the same dilutions ($P < 0.05$).

Kotake-Nara et al.[184] analyzed the effects of different lycopene concentrations on the cell viability of three human prostate cancer cell lines—PC-3, DU-145, and LNCaP. Lycopene was isolated from a tomato oleoresin (Lyc-O-Mato 6%) to a purity of >99%. Lycopene supplementation at 20 μmol/L significantly reduced cell viability to 58.7% and 54.1% of the control culture for the PC-3 ($P < 0.01$) and the DU-145 cell lines ($P < 0.01$), respectively, after 72 hours of cultivation. Lycopene supplementation at 5 μmol/L and 10 μmol/L also significantly reduced cell viability in the PC-3 ($P < 0.01$) and the DU-145 ($P < 0.01$) cell lines after 72 hours of cultivation. However, cell viability was not reduced in the LNCaP cell line with 5, 10, or 20 μmol/L lycopene supplementation after cultivation for 72 hours. Pastori et al.[185] examined the effects of various lycopene and α-tocopherol combinations on the PC-3 and the DU-145 cell lines. Synthetic lycopene (95%, all *E*) was utilized in this study. Lycopene at 1 μM with α-tocopherol at 50 μM resulted in a strong inhibitory effect on human prostate carcinoma cell proliferation. After supplementation with lycopene plus α-tocopherol, PC-3 and DU-145 cells were inhibited by 40% and 88%, respectively, compared to their corresponding control cultures after 24 hours of cultivation. The study authors also observed a dose-dependent inhibition of these cell lines with increasing lycopene concentrations (up to 1 μM only) and a constant α-tocopherol concentration of 50 μM.

Risk Analysis

Bosetti et al.[186] analyzed the consumption of five food groups/items (milk and dairy products, butter, seed oils, raw tomatoes, and cooked tomatoes) on the risk of developing prostate cancer based on the results from Tzonou et al. 1999. Only those food groups/items from the previous study that were associated with $P \leq 0.10$ and had the support of converging scientific evidence were examined. After each food group/item was categorized into marginal tertiles of either lower (-1), middle (0), or higher (+1) levels of consumption, an overall dietary score was calculated for each subject. The overall dietary score was obtained by adding the values of those food groups/items positively associated with prostate cancer risk (milk and dairy products, butter, and seed oils) and then subtracting those food groups/items negatively associated with prostate cancer risk (raw tomatoes and

cooked tomatoes). Overall dietary scores were further categorized into quintiles (-5 to +5) representing increasing levels of prostate cancer risk as a function of food group/item consumption. Bosetti et al. observed a gradual increase in risk of prostate cancer with increasing values of overall dietary score ($P < 0.001$). In other words, the highest overall dietary score of +5 (high milk and dairy product, butter and seed oil intake/low raw and cooked tomato intake) corresponded to the highest risk of prostate cancer. The lowest overall dietary score of -5 (high raw and cooked tomato intake/low milk and dairy product, butter and seed oil intake) corresponded to the lowest risk of prostate cancer. The study authors also determined that if all individuals were shifted to the lowest risk category (except for those already in this category), then incidence of prostate cancer would be reduced by 41% in this study population. A more modest 19% reduction in prostate cancer incidence would be achieved if all individuals were shifted to the adjacent lower risk category (except for those already in the lowest category).

Abstracts

A recently published abstract discusses the preliminary findings of lycopene supplementation on the angiogenesis of human microvascular endothelial cells (HMVEC) *in vitro*. Angiogenesis is the process through which biologically active tissue develops new capillary networks. This improves the oxygen and nutrient status of the tissue. Cyclooxygenase-2 (COX-2), an enzyme-protein complex, is active during angiogenesis.[187] According to Liu et al.,[188] the total number of tube-like structures was significantly reduced with 1 μM of lycopene supplementation compared to the control culture ($P = 0.03$). The total length of tube-like structures was also significantly reduced with 1 μM of lycopene supplementation ($P = 0.004$). These results suggest a possible role for lycopene in reducing prostate tumor growth.

Design Type Four Studies

Study	Sample Size	Quality	Results†
Boileau, T, Liao, Z, Kim, S, Lemeshow, S, Erdman, J, and Clinton, S. "Prostate carcinogenesis in *N*-methyl-*N*-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets." *Journal of the National Cancer Institute* 2003; 95:1578-86.	194	+	**SS** (for tomato powder supplementation only)
Bosetti, C, Tzonou, A, Lagiou, P, Negri, E, Trichopoulos, D, and Hsieh, C. "Fraction of prostate cancer incidence attributed to diet in Athens, Greece." *European Journal of Cancer Prevention* 2000; 9:119-23.	566 Cases: 320 Controls: 246	+	**SS**

Guttenplan, J, Chen, M, Kosinska, W, Thompson, S, Zhao, Z, and Cohen, L. "Effects of a lycopene-rich diet on spontaneous and benzo[*a*]pyrene-induced mutagenesis in prostate, colon and lungs of the *lacZ* mouse." *Cancer Letters* 2001; 164:1-6.	36	+/∅	**SN**
Imaida, K, Tamano, S, Kato, K, Ikeda, Y, Asamoto, M, Takahashi, S, Nir, Z, Murakoshi, M, Nishino, H, and Shirai, T. "Lack of chemopreventive effects of lycopene and curcumin on experimental rat prostate carcinogenesis." *Carcinogenesis* 2001; 22:467-72.	Experiment 1: Unknown Experiment 2: 120 Experiment 3: 105	∅	**N/A**[#]
Kim, L, Rao, A, and Rao, L. "Effect of lycopene on prostate LNCaP cancer cells in culture." *Journal of Medicinal Food* 2002; 5:181-7.	Unknown	+	**SS**
Kotake-Nara, E, Kushiro, M, Zhang, H, Sugawara, T, Miyashita, K, and Nagao, A. "Carotenoids affect proliferation of human prostate cancer cells." *Journal of Nutrition* 2001; 131:3303-6.	Unknown	∅	**SS**
Liu, L, Meydani, M, and Rodriguez, S. "Lycopene suppresses angiogenesis of human microvascular endothelial cells (HMVEC) *in vitro* **(abstract)**." *FASEB Journal* 2003; 17:4-5.	Unknown	N/A	**SS**
Mucci, L, Tamimi, R, Lagiou, P, Trichopoulou, A, Benetou, V, Spanos, E, and Trichopoulos, D. "Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system?" *BJU International* 2001; 87:814-20.	112	+	**SS**
Pastori, M, Pfander, H, Boscoboinik, D, and Azzi, A. "Lycopene in association with α-tocopherol inhibits at physiological concentrations proliferation of prostate carcinoma cells." *Biochemical and Biophysical Research Communications* 1998; 250:582-5.	Unknown	+/Ø	**SS**

Richards, L, Benghuzzi, H, Tucci, M, and Hughes, J. "The synergistic effect of conventional and sustained delivery of antioxidants on LNCaP prostate cancer cell line." *Biomedical Sciences Instrumentation* 2003; 39:402-7.	Unknown	+/∅	SS

†SS (support, significant)
SN (support, not significant)
N (not support)

#This study consisted of three separate animal experiments. Since the results concerning lycopene supplementation on the risk of prostate cancer varied between experiments, this study was classified as N/A in all 'Results' sections within this review.

b. Quality Ratings

Table 1. Summary of Quality Ratings and Results

Design Type	Quality				Total	Results				Total
	+	+/∅	∅	N/A		SS	SN	N	N/A‡	
1	0	2	1	0	3	3	0	0	0	3
2	3	2	0	1	6	4	0	2	0	6
3	5	12	6	0	23	8†	3	11	1	23
4	4	3	2	1	10	8§	1	0	1	10
Total	12	19	9	2	42	23	4	13	2	42

† Gann et al. and Vogt et al. found a significant risk reduction for aggressive cancers only. The results for Jain et al. found that only overall tomato consumption was associated with a significantly lower risk of prostate cancer.
§ Boileau et al. found that only tomato powder supplementation was associated with a significantly lower risk of prostate cancer.
‡ The following studies were included as N/A in the Summary of Results above and were not included in the Summary of Quality Ratings below because they could not be classified according to the summary categories (SS, SN, N):

Hayes, R, Ziegler, R, Gridley, G, Swanson, C, Greenberg, R, Swanson, G, Schoenberg, J, Silverman, D, Brown, L, Pottern, L, Liff, J, Schwartz, A, Fraumeni, J, and Hoover, R. "Dietary factors and risks for prostate cancer among blacks and whites in the United States." *Cancer Epidemiology, Biomarkers and Prevention* 1999; 8:25-34.

Imaida, K, Tamano, S, Kato, K, Ikeda, Y, Asamoto, M, Takahashi, S, Nir, Z, Murakoshi, M, Nishino, H, and Shirai, T. "Lack of chemopreventive effects of lycopene and curcumin on experimental rat prostate carcinogenesis." *Carcinogenesis* 2001; 22:467-72.

Table 2A. Summary of Quality Ratings: Studies that Support Hypothesis with Significant Results (SS)

Design Type	Quality				Total
	+	+/∅	∅	N/A	
1	0	2	1	0	3
2	3	0	0	1	4
3	2	4	2	0	8
4	4	2	1	1	8
Total	9	8	4	2	23

Table 2B. Summary of Quality Ratings: Studies that Support Hypothesis with Non-Significant Results (SN)

Design Type	Quality				Total
	+	+/∅	∅	N/A	
1	0	0	0	0	0
2	0	0	0	0	0
3	0	3	0	0	3
4	0	1	0	0	1
Total	0	4	0	0	4

Table 2C. Summary of Quality Ratings: Studies that Do Not Support Hypothesis (N)

Design Type	Quality				Total
	+	+/∅	∅	N/A	
1	0	0	0	0	0
2	0	2	0	0	2
3	3	5	3	0	11
4	0	0	0	0	0
Total	3	7	3	0	13

c. CONSUMER UNDERSTANDING

Consumer research was conducted to provide information about consumers' awareness, perception, and judgment regarding qualified health claims. The sample was derived from the NFO panel consisting of 750 male and female adults who have eaten processed tomato products (i.e. ketchup, pasta sauce) in the past 6 months. The study sample was nationally representative of adults in the U.S. and included a sample of at least 80 males over the age of 40. The study used three different qualified health claims about a relationship between consumption of lycopene in tomato products and reduced risk of prostate cancer to test consumer understanding of and reaction to example claims. The three tested qualified health claims were as follows:

A. Consumption of processed tomato products like ketchup, pasta sauce, tomato juice, or tomato soup, as part of a healthy diet, may reduce the risk of prostate cancer.

B. Although evidence is not yet conclusive, studies show that consumption of processed tomato products like ketchup, pasta sauce, tomato juice, or tomato soup, as part of a healthy diet, may reduce the risk of prostate cancer.

C. Growing scientific evidence would suggest that consumption of processed tomato products like ketchup, pasta sauce, tomato juice, or tomato soup, as part of a healthy diet, may reduce the risk of prostate cancer.

Interviewers also asked if the example health claims would motivate them to change or rethink their eating habits and in what ways.

The results show that 45% of adults are aware of lycopene. Among those who are aware of lycopene, 60% believe that it is found in tomatoes and tomato products. Others believe that it is found in vegetables (10%) and/or fruits (11%), while 25% do not know which foods contain lycopene. Among those aware of lycopene, Claim A received significantly fewer positive comments (74% vs. 83% and 84%) than Claim B and Claim C. Furthermore, Claim A received a significantly higher number of negative comments than Claim B. This was mainly driven by a combination of respondents perceiving that the general statement in Claim A is not true and/or that processed foods can not be healthy. Across all three claims, the majority of respondents agreed that they would "incorporate more tomato products into diet" and that "lycopene is not an additive". For all three claims, the majority of respondents believed they would have to eat tomato products 1-2 times/day or 1-2 times/week in order to realize a reduction in risk. The statement that respondents agreed with most was that lycopene "Will reduce the risk of prostate cancer", whereas only 1% felt that it would "Cure prostate cancer." These results indicate that there is a growing awareness of lycopene and that the majority of people are not misled by the tested qualified health claims.

d. Relevance for Disease Reduction in Target Population Risk Assessment

Nutrient Contribution of Tomatoes

Fresh and processed tomatoes are an important dietary source of nutrients among U.S. adults. In a study identifying major food sources of 27 nutrients using data from USDA's 1989-91 CSFII, tomatoes ranked in the top 10 food sources of fiber, vitamin A, vitamin C, vitamin E, carotenes, vitamin B-6, potassium, iron, magnesium and copper[4]. Tomatoes were in the top 15 food sources for folate, thiamin and niacin. Specific rankings are shown in Table 3. (See Appendix A for

additional information about tomato consumption in the U.S. and lycopene concentration in specific tomato products.)

Table3. Tomatoes Ranked as Food Sources of Nutrients.

Nutrient	Rank of Tomatoes	Contribution of Food Group to Nutrient
Fiber	5	5.7%
Vitamin C	2	9.3%
Vitamin E	5	5.8%
Vitamin A	7	3.9%
Carotenes	2	8%
Vitamin B-6	7	3.4%
Potassium	5	5.9%
Iron	8	2.6%
Magnesium	9	3.1%
Copper	3	6.1%
Folate	12	2.0%
Thiamin	13	2.1%
Niacin	11	2.2%

Data and Methods

The data for this analysis were from the Continuing Survey of Food Intake by Individuals, 1994-96, 1998 (CSFII). Tomato consumption was estimated using the CSFII individual food file and food codes for tomato products including raw tomatoes, cooked tomatoes, tomato juices, tomato sauces (a broad category covering ketchup, salsa, spaghetti sauce, barbecue sauce, etc.), tomato mixtures (such as tomato and corn, tomato and okra, etc.), and tomato soups. Consumption of tomato products in mixtures, such as lasagna, was estimated by calculating the percentage by weight of each tomato product category contained in CSFII mixture database. This information was then merged to the individual food file. The weight of the individual food item consumed was multiplied by the percentage by weight of each tomato product category to calculate the grams of each tomato product category in mixtures.

The tomato product consumption categories were then aggregated back up to the individual level, and a two-day average was calculated for each tomato product category. Lycopene concentration values were added to the data using typical lycopene concentration values for the category based on the USDA National Nutrient Database for Standard Reference, SR 16. The values used for each category were:

Tomato Product Category	Lycopene Concentration (µg/g)	Food Used for Estimate (ndb_no)
Raw Tomatoes	25.73	Tomatoes, red, ripe, raw, year round average (11529)
Cooked Tomatoes	30.41	Tomatoes, red, ripe, cooked (11530)
Tomato Juices	90.37	Tomato juice, canned, with salt added (11540)
Tomato Sauces	151.52	Tomato products, canned, sauce (11549)
Tomato Mixtures	166.77	Tomato products, canned, sauce, with mushrooms (11551)
Tomato Soups	50.84	Soup, tomato, canned, prepared with equal volume milk, commercial (06359)

Estimates of consumption of lycopene in tomato products were then calculated for adult males (over 18). Using these assumptions, the mean consumption of lycopene in tomato products was 6.9 mg/day. This is likely to be an overestimate because we are applying a high value for lycopene concentration (151.52 µg/g, the value for canned tomato sauce) to a broad range of tomato sauces and could be improved by matching the lycopene concentration values for specific foods to specific food codes in the individual food file. However, for the purposes of this simulation that refinement should not make a large difference. The estimates in this model are used to generate the shape of the distribution of consumption of lycopene in tomato products and the relative location (by quintile) of simulated individuals. The relative risk factors are also based on quintiles and not specific values of lycopene consumption. The key for the simulation is to identify the relative position of individuals on the basis of lycopene consumption. The actual level of consumption will have little effect on the results and the model is not intended to provide an estimate of actual consumption of lycopene in tomato products.

Design of Simulation

The lycopene consumption estimates from CSFII were used as an input to a simple simulation model of prostate cancer risk. The simulation model of prostate cancer risk began with a randomly generated value for lycopene consumption. The randomly generated value was drawn from a probability distribution fit to the actual distribution estimated from CSFII. Because of the highly skewed nature of the distribution, we excluded the lower and upper deciles for the purposes of estimating a probability distribution. Using the estimated lycopene consumption of adult males in the 10^{th} through the 90^{th} percentile of lycopene consumption, a probability distribution of lycopene consumption was

estimated in @Risk™. The selected probability distribution for the simulation was an exponential distribution. This value is referred to in the model as **BASE**.

The value of **BASE** is used to place a simulated individual in a relative risk category, **RR**, based on the estimates from Giovannucci, et.al. 1995. The RR values from Giovannucci were normalized so that simulated individuals in the third quintile had a RR of 1.0. This created RR values of 1.06 for individuals in Q1, 0.96 for Q2, 1.0 for Q3, 0.95 for Q4, and 0.84 for Q5. Note that there is a slight increase in relative risk for prostate cancer as an individual moves from Q2 to Q3. This is true in the original Giovannuccii, et.al. 1995 paper also. The difference in relative risk between the two categories is very small.

Changes in consumption of tomato products, which contain lycopene, **WEEKLY**, were calculated based on a one serving (1 cup) per week increase in consumption of spaghetti sauce (39.957 mg of lycopene per serving, an average increase of 5.71 mg/day). For comparison purposes, the impact of a change of one serving of spaghetti sauce per day was also calculated, but those results are only briefly discussed. The increase in lycopene consumption is assumed to result from the addition of a qualified health claim to the label of tomato products. This assumption is supported by consumer research that demonstrates that consumers say a qualified health claim would prompt them to increase their consumption of tomato products.

Simulated individuals were then assigned an alternative **RR** based on the new quintile they would be in based on their total lycopene consumption (**BASE + WEEKLY,** hereafter **BASE PLUS**). Because of the relatively low levels of lycopene consumption estimated from CSFII and the relatively high lycopene consumption of a serving of spaghetti sauce, most simulated individuals were moved into Q5 regardless of which quintile they were in at **BASE**.

The relative risk rating was multiplied by a **Generic Prostate Cancer Risk** of 0016, based on the American Cancer Society, Surveillance Research, 2003 factor for estimating expected community prostate cancer cases.

The product of the **RR** and the **Generic Prostate Cancer Risk** yielded a probability of prostate cancer for each simulated individual, **Pr(Prostate Cancer)**. Two values of **Pr(Prostate Cancer)** were calculated for each individual: one for **BASE** and one for **BASE PLUS**).

For each simulated individual, a random number was drawn from a uniform distribution between 0 and 1. This random variable was named **NATURE**. This value was compared to the two values for **Pr(Prostate Cancer)** (the value for **BASE** and the value for **BASE PLUS**). If **Pr(Prostate Cancer)** was greater than or equal to **NATURE**, the simulated individual was assigned to the category representing a new simulated case of prostate cancer, otherwise they were

assigned to the category representing those who did **not** develop a new simulated case of prostate cancer.

The basic structure of the prostate cancer risk simulation is shown in the schematic design in Figure 1 titled "Structure of Prostate Cancer Risk Simulation." The probability distributions for the simulated risks of prostate cancer and the statistics for the number of new cases of prostate cancer are presented below.

Figure 1
Structure of Prostate Cancer Risk Simulation

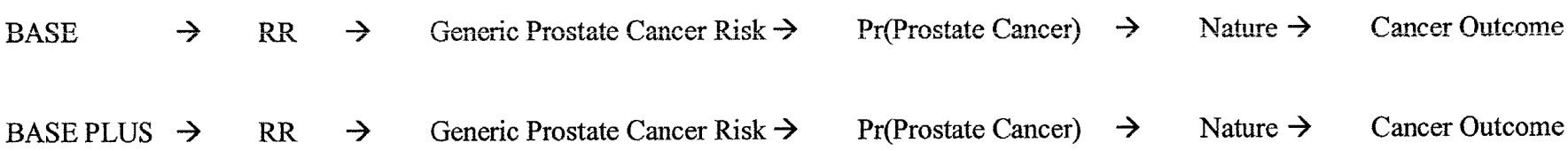
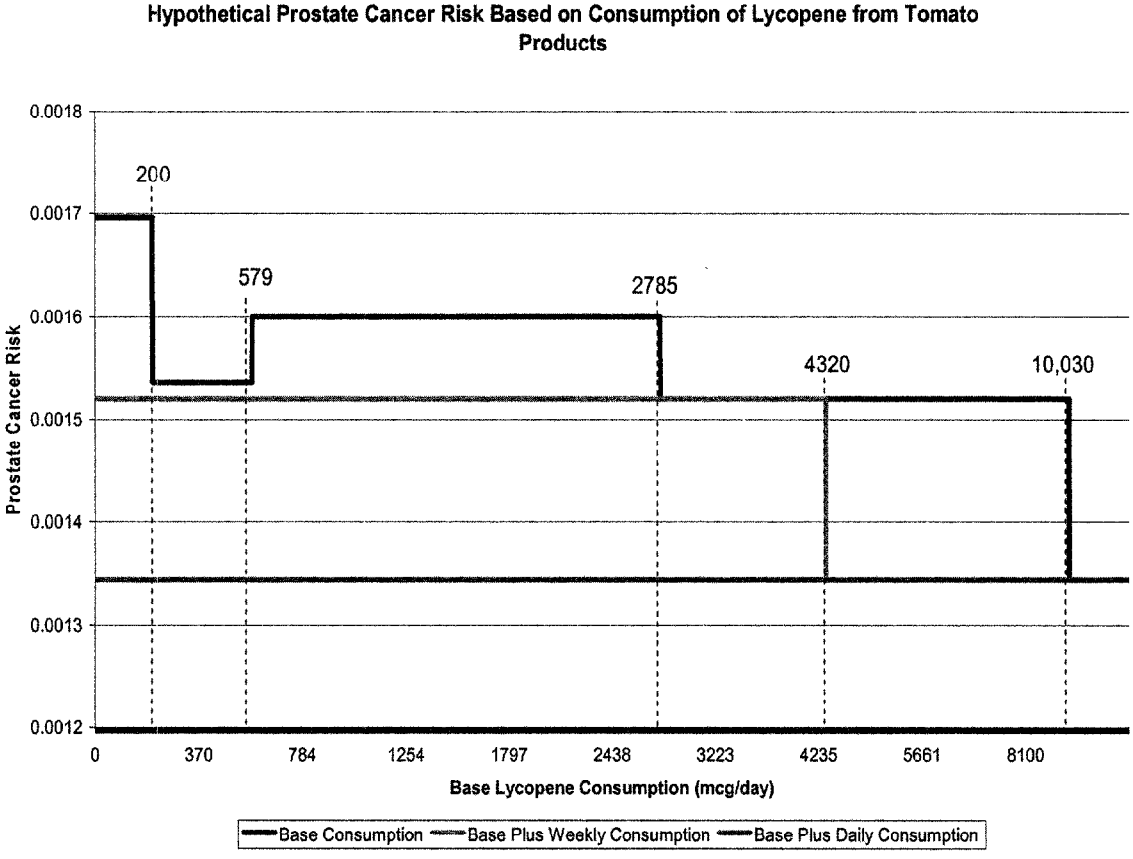


Figure 2 shows the risk that a simulated individual will develop a new case of prostate cancer in one iteration of the model based on their initial simulated consumption of tomato products, which contain lycopene (BASE). The graph exhibits a "step function" because of the way the model uses quintiles of consumption to assign relative risks. The graph contains three lines: one for BASE consumption of lycopene, one for BASE consumption plus one additional serving of spaghetti sauce per week, and one for BASE consumption plus one additional serving of spaghetti sauce per day. BASE plus daily consumption is a flat line with the lowest risk of prostate cancer (0.00135) because all individuals who add an additional serving of spaghetti sauce per day will be moved into the upper quintile, even if they were non-consumers before. BASE plus weekly consumption has only one step. Those who originally consumed less than 4320 mcg/day have a prostate cancer risk of 0.00152 because the additional serving spaghetti sauce moves them to the fourth quintile. Those who originally consumed more than 4230 mcg/day have a prostate cancer risk of 0.00135 because they are moved to the fifth quintile. The line for BASE consumption with no additional spaghetti sauce has five steps representing all five quintiles. Prostate cancer risk in this group ranges from 0.00170 to .00135.

Figure 2
Hypothetical Prostate Cancer Risk Based on Consumption of Lycopene in Tomato Products



The simulation also demonstrates a reduction in the number of new prostate cancer cases reported if consumption of tomato products is increased. Among the BASE simulations, 157 new cases of prostate cancer were generated compared to 147 among the BASE PLUS WEEKLY group and 135 in the BASE PLUS DAILY group. Using the more conservative BASE PLUS WEEKLY comparison, 10 new cases of prostate cancer were prevented, a little more than a 6 percent reduction. If this is extrapolated to the approximately 100 million adult men in the U.S. population, this dietary change could potentially reduce the number of new prostate cancer cases by 10,000.

In conclusion, a reasonable increase in consumption of tomato products—one cup of spaghetti sauce per week in this example—could lead to a reduction in the number of new prostate cancer cases. Using the assumptions of this risk assessment, the change in diet could reduce the number of new prostate cancer cases by approximately 10,000.

Limitations

These results should be interpreted with some caution. The risk assessment generally uses conservative estimates of the potential impact of tomato products on reduced risk of prostate cancer. For example, the model assumes that there is no further reduction in the relative risk of prostate cancer once consumption of lycopene in tomato products passes 10mg/day. It is possible that levels of consumption in excess of 10mg/day would reduce the relative risk to levels lower than those assumed here. The model also focuses on a reasonable increase in tomato product consumption corresponding to an increase of just one serving of spaghetti sauce per week. We believe this level is achievable in typical diets based on the consumer research presented in this dossier. Nevertheless, despite these conservative assumptions the model is only as good as the assumptions which drive it. Further data on lycopene consumption patterns, changes in lycopene consumption as a result of a qualified health claim, and the stronger evidence for the relative risks of differing levels of consumption of tomato products, which contain lycopene, could increase the reliability of the simulation.

The simulation could also be improved by adding other relevant factors. Two additional variables are particularly important: age and race/ethnicity. Replace the **Generic Prostate Cancer Risk** with an **Age and Race Adjusted Prostate Cancer Risk would** more accurately reflect reality and allow the exploration of differential impacts of increased tomato product consumption in particular sub-populations.

Despite these limitations, we believe this simulation demonstrates that using conservative assumptions and reasonable increases in the consumption of tomato products could produce a modest but meaningful reduction in prostate cancer for the target population.

V. DISCUSSION

In addition to the classification of study type described in the interim guidance, it is informative to divide the studies into prospective studies, case-control studies, and intervention trials. This categorization affords another perspective in judging the weight of scientific evidence regarding the relationship between consumption of tomato products, which contain lycopene, and the risk of prostate cancer.

The literature search yielded several prospective observational cohort studies that, in general, support a possible relationship between total lycopene intake or consumption of tomato products and reduced risk of prostate cancer. The prospective studies are summarized below.

Prospective Studies

Tested Relationship	Study	Cases/ Controls	Results	*P* for trend
Dietary Lycopene and Prostate Cancer			Lycopene Intake (Low to High)	
	Giovanucci, 2002	2481/47,365	1.00 1.03 0.99 0.97 0.84	0.003
	Giovanucci, 1995	773/47,894	1.00 0.90 0.94 0.89 0.79	0.04
Cooked Tomatoes and Prostate Cancer Risk			Cooked Tomato Intake (Low to High)	
	Giovanucci, 2002			
	(Total)	2481/47,365	1.00 0.96 0.80 0.77	<.001
	(Stage A&B)	1320	1.00 0.86 0.63 0.72	<.001
	(Stage C&D)	354	1.00 0.99 0.77 0.65	0.02
	Giovanucci, 1995			
	(Total)	773/47,894	1.00 0.92 0.78 0.85 0.65	0.01
	(Stage C&D)	271	1.00 1.15 0.86 0.88 0.47	0.03
Tomatoes and Prostate Cancer Risk			Tomato Intake	
	Mills, 1989	180/35,000	Multivariate RR=0.60 for ≥5 times/week	0.02
	Schuurman,			
	1998	58,279		
	2002	58,279		
Prediagnostic serum lycopene and risk of prostate cancer			Blood lycopene (Low to High)	
	Nomura, 1997	142/142	1.0 1.0 1.0 1.1	0.86
	Hsing, 1990	103/103	1.00 0.81 0.55 0.50	0.04
	Gann, 1999	578/1294	1.00 0.89 0.90 0.87 0.75	0.12
	(Aggressive cancer)	(259/1294)	1.00 0.64 0.71 0.70 0.56	0.01
	Huang, 2003			
	(CLUE I)	(182/364)	1.00 0.86 0.74 0.96 0.83	0.72
	(CLUE II)	(142/284)	1.00 0.88 0.77 0.83 0.79	0.49
	Goodman, 2003	205/483	1.00 0.65 0.47 1.04	0.83
Serum lycopene and prostate cancer			Serum lycopene (Low to High)	
	Vogt, 2002	204/228	1.00 0.97 0.74 0.65	0.09
	(Non-aggressive)		1.00 1.05 0.72 0.79	0.36
	(Aggressive)		1.00 0.93 0.79 0.37	0.04
	Lu, 2001	65/132	1.00 0.67 0.29 0.17	0.005
	Rao, 1999	12/12	Cases mean: 244 Controls mean: 433	0.0004

The literature search also generated numerous case-control studies but the results of these were less supportive of a protective role of lycopene in tomato products. The case-control studies are summarized below.

Case-Control Studies

Tested Relationship	Study	Cases/ Controls	Results	*P* for trend
Dietary Lycopene and Prostate Cancer			Lycopene Intake (Low to High)	
	Cohen, 2000	628/602	1.0 0.93 1.23 0.89	0.96
	Norrish, 2000	317/480	1.0 .077 0.86 0.76	0.3
	Deneo-Pellegrini, 1999	175/233	1.0 1.16 0.80 1.20	0.9
	Jain, 1999	617/636	1.0 0.80 0.80 1.01	--
	Key, 1997	328/328	1.0 0.90 0.99 ----	
	LeMarchand, 1991			
	<70 yrs	452/899	1.0 1.4 1.3 0.9	0.35
	>70 yrs	452/899	1.0 1.0 1.1 1.1	0.57
Cooked Tomatoes and Prostate Cancer Risk			Cooked Tomato Intake (Low to High)	
	Kolonel, 2000			
	Total	1619/1618	1.00 1.07 1.11 0.79 0.94	0.56
	Advanced	514/1618	1.00 1.12 1.13 0.80 0.96	0.76
	Cohen, 2000	628/602	1.00 0.97 0.90	0.68
	Norrish, 2000	317/480	1.00 0.97 0.85 0.82	0.30
	Hayes, 1999			
	Total	932/1201	1.0 1.2 0.8 1.0 1.3	0.71
	Advanced		1.0 1.8 1.4 1.6 1.6	0.95
	Jain, 1999 (*total tomatoes)	617/636	1.00 0.77 0.78 0.64	(95% CI: 0.45-0.91)
	Tzonou, 1999	320/246	1.00 0.85 0.55	0.03
	Key, 1997	328/328	1.00 0.77 0.99 0.92	0.64
Tomatoes and Prostate Cancer Risk			Tomatoes and tomato juice intake Low to High	
	Villeneuve, 1999	1623/1623	1.0 1.1 0.9 1.0	0.29
	Whittemore, 1995	1655/1645	No associations were seen between risk and consumption of certain types of food, including vegetables.	
Lycopene intake and Genotype	Van Gils, 2002	260	Prostate cancer risk was highest among men who were homozygous for the common allele at	

			codon 399 and had low dietary intake of lycopene (OR = 2.0; 95% CI = 0.8 to 4.9; P_{trend} = 0.13), whereas low intake of lycopene in men without this genotype hardly increased prostate cancer risk (OR = 1.0; 95% CI = 0.4 to 2.4; P_{trend} = 0.98).
Cooked tomatoes and IGF-1 level	Mucci, 2001	112/112	Consumption of cooked tomatoes was significantly inversely associated with IGF-1 levels, with a mean (95% CI) change of -31.5% (-49.1 to -7.9) for an increment of one serving per day.

A review of the scientific literature examining the relationship between lycopene intake and prostate cancer risk yielded very few randomized, controlled intervention trials. The following intervention trials examined the relationship between lycopene intake and prostate cancer in men who had already been diagnosed with prostate cancer. Although these three studies are relatively well-designed and demonstrate an inverse relationship between lycopene supplementation and prostate cancer progression via direct or indirect assessment, they are limited in that they do not study the relationship between lycopene consumption and prostate cancer prevention.

Intervention Trials

Tested Relationship	Study	Cases	Results	*P* for trend
Randomized Control Trial	Kucuk, 2001	26	<u>Plasma PSA levels</u> Treatment group: 18% decrease Control group: 14% increase	0.25
	2002 (Tomato Oleoresin Supplement)	35	Mean plasma PSA levels were lower in treatment group.	
	Ansari, 2003 (tomato sauce)	54	After 2 years, reduction in PSA level was greater in the orchidectomy and lycopene group.	<0.001
Non-randomized Intervention Trial	Chen, 2001	32	After the dietary intervention (consuming 30 mg of lycopene per day for 3 weeks), Compared with preintervention levels, leukocyte oxidative DNA damage was significantly reduced after the intervention, from 0.61 8-OHdG/10^5 dG (95% CI=0.45-0.77 8-OHdG/10^5 dG) to 0.48 8-OHdG/10^5 dG (95% CI=0.41-0.56 8-OHdG/10^5 dG) (P=0.005). Prostate tissue oxidative damage was significantly lower in men who had the intervention (0.76 8-OHdG/10^5 dG [95% CI=0.55-0.96 8-OHdG/10^5 dG]) than in randomly selected patients (1.06 8-OHdG/10^5 dG [95% CI=0.62-1.51 8-OHdG/10^5 dG] P=0.03). Serum PSA levels decreased after the intervention, from 10.9 ng/mL (95% CI=8.7-13.2ng/mL) to 8.7 ng/mL (95% CI=6.8-10.6 ng/mL) (P<.001).	
	Bowen, 2002	32	Serum and prostate lycopene concentrations increased 1.97- and 2.92-fold (*P*<0.001), respectively, after tomato sauce consumption. Mean serum PSA	

			concentrations decreased by 17.5% ($P<0.002$) and leukocyte 8OHdG decreased by 21.3% ($P<0.005$) after tomato sauce consumption. Resected tissues from tomato sauce-supplemented patients had 28.3% lower prostate 8OHdG compared with nonstudy control group ($P<0.03$). Cancer cell 8OHdG staining of Gleason Score-matched resected prostate sections was reduced by 40.5% in mean nuclear density ($P<0.005$) and by 36.4% in mean area ($P<0.018$) compared with the presupplementation biopsy. Apoptotic index was higher in hyperplastic and neoplastic cells in the resected tissue after supplementation.

The lack of significant results in many of the studies may be explained by small sample sizes, little variability in lycopene consumption levels, dietary assessment inaccuracies due to self-reporting bias and challenges in estimating usual intake, and model specification differences. Lycopene bioavailability differences may also complicate interpretation and comparison of results. The relationship between estimated lycopene intake and serum lycopene is very poor, with correlation coefficients of between 0.1 and 0.35 in different populations.[189]

More research is needed to clarify the role of lycopene in tomato products in reducing prostate cancer risk and prostate cancer progression. There are several ongoing trials examining the relationship between lycopene in tomato products and prostate cancer. NCI is currently conducting a phase 1 study of lycopene for the chemoprevention of prostate cancer as well as a pilot study of isoflavones versus lycopene prior to radical prostatectomy in patients with localized prostate cancer.

Overall Ranking

The overall ranking of the strength of the body of the evidence was based upon three criteria: quantity (including both number of studies and number of observations), consistency, and relevance to disease risk reduction in the target subgroup.

There were a total of three Type 1 studies (randomized interventions) that reported a statistically significant reduction in the risk of prostate cancer for high consumption of tomato products, which contain lycopene. Two studies were classified as adequate with some uncertainties existing, and one was classified as uncertainties exist. However, the subjects in all of these studies were already diagnosed with prostate cancer, so the relevance of these studies for a claim that tomato products, which contain lycopene, reduces the risk of prostate cancer is limited.

There were three adequate Type 2 studies and one N/A (an abstract) that reported a statistically significant reduction in the risk of prostate cancer for high consumption of tomato products, which contain lycopene. These included the Mills et al. study of Seventh-Day Adventists and the two Giovannucci et al. studies that utilized the Health Professionals Follow-up Study. There were also two studies by Schuurman et al. of a large prospective cohort in the Netherlands that found no relationship between consumption of tomato products and risk of prostate cancer. However, the authors reported that misclassification of fruit and vegetable consumption likely led to an underestimation of the strength of these associations.

There were a total of eight Type 3 studies that showed a statistically significant reduction in the risk of prostate cancer for high consumption of tomato products, which contain lycopene. Two were adequate, four were classified as adequate with some uncertainties existing and two received ratings of some uncertainties exist. Eight Type 4 studies showed a statistically significant reduction in prostate cancer risk with high consumption of tomato products, which contain lycopene. One received an adequate rating. There were a total of 23 studies with statistically significant results used to formulate the report, with 17 of them receiving ratings of adequate or adequate with some uncertainties existing.

The total number of studies evaluated was 42. The studies covered a variety of sample sizes, however there were only a total of three Type 1 studies evaluated with a combined total of 115 subjects. Therefore CFNP gave the quantity of evidence a 2 out of 3-star rating.

In terms of consistency, approximately 64% of the studies reported results that supported the hypothesis. Twenty-three studies which supported it were statistically significant and four were not. Studies that found no association often had small sample sizes and/or low doses of lycopene from tomato products. Based on the above factors CFNP gave consistency a 3 out of 3-star rating.

VI. CONCLUSION AND RECOMMENDATION

In the opinion of the Center for Food and Nutrition Policy at Virginia Tech in Alexandria, the body of evidence supports a qualified health claim that consumption of tomato products, which contain lycopene, reduces the risk of prostate cancer. CFNP believes the body of evidence corresponds most closely to the criteria that FDA has established for a Second Level or 'B' claim. The FDA's suggested qualifying language for a 'B' claim is "[a]lthough there is scientific evidence supporting the claim, the evidence is not conclusive."

At this time, the evidence does not meet the standard of significant scientific agreement, so an 'A' claim is not appropriate. To support an 'A' claim, the body of evidence would need to include more definitive clinical trials demonstrating a protective effect for consumption of tomato products, which contain lycopene, and more evidence from prospective observational studies. In particular, it would be useful to have additional epidemiological evidence from U.S. prospective observational studies other than the Health Professionals Follow-up Study.

A 'B' level claim is defined by the FDA as a moderate/good level of comfort among qualified scientists that the claimed relationship is scientifically valid. The second level is "promising," but not definitive. High to moderate quality studies of study design Types 1 and 2 and sufficient numbers of individuals would be tested to result in a moderate degree of confidence that results could be extrapolated to the target population. Additionally, studies of similar or different design would generally result in similar findings and the benefit would reasonably be considered to be physiologically meaningful and achievable under intake and use conditions that are appropriate for such conventional human food and dietary supplements that would be the subject of the claim.

Criteria for the third level or 'C' claim include maintaining a low consistency with statements from authoritative bodies or being ranked as "low" in terms of scientific support by qualified scientists. The claim must be based mostly on moderate to low quality studies of study design Type 3, and insufficient numbers of individuals would be tested. Additionally, studies of different design would generally result in similar findings but uncertainties would exist. Uncertainties would also exist as to whether the benefit would be considered physiologically meaningful and achievable under intake and use conditions that are appropriate.

The body of evidence reviewed in this report includes multiple prospective observational studies of high quality that support the proposed claim. Furthermore, there are some

randomized clinical trials that provide evidence that is consistent with a reduced risk of prostate cancer, but these Type 1 studies have limitations that are discussed in detail in the full report. The overall body of evidence from all types of studies supports the proposed qualified health claim, and only one study presents any evidence of a possible increased risk of prostate cancer.

Plausible mechanisms of action have been proposed and demonstrated in *in vitro* and animal models. The validity of the prospective observational studies is increased because there is theoretical and empirical evidence to explain the observed relationship found in the epidemiological data.

Increased consumption of tomato products is relevant for reduction of prostate cancer risk among adult males. The evidence suggests that reasonable increases in tomato product consumption could lead to a modest, but meaningful, reduction in the disease burden from prostate cancer.

There is no reason to believe that any harm could result from the proposed qualified health claim. Tomato products are GRAS and there is no evidence of toxicity at any reasonable level of consumption. (Please see Appendix B for suggested intake levels of lycopene in tomato products.)

The proposed health claim is consistent with existing authoritative dietary guidance recommending consumption of five or more servings of fruits and vegetables per day. Consumer research shows that consumers will not be misled by the proposed qualified health claim. The research demonstrates that consumers will understand the proposed qualified health claim and respond by increasing their consumption of tomato products.

Therefore, CFNP believes that the body of evidence on the relationship between tomato products which contain lycopene and risk of prostate cancer supports a 'B' claim based on the criteria established by FDA.

Proposed Claims

- Although the evidence is not conclusive, tomato lycopene may reduce the risk of prostate cancer.
- Although the evidence is not conclusive, tomato lycopene may reduce the risk of prostate cancer when consumed as part of a healthy diet.
- Although the evidence is not conclusive, tomato products, which contain lycopene, may reduce the risk of prostate cancer.
- Although the evidence is not conclusive, tomatoes and tomato products, which contain lycopene, may reduce the risk of prostate cancer.
- Although the evidence is not conclusive, tomato products, which contain lycopene, may reduce the risk of prostate cancer when consumed as part of a healthy diet.
- Although the evidence is not conclusive, tomatoes and tomato products, which contain lycopene, may reduce the risk of prostate cancer when consumed as part of a healthy diet.
- Although the evidence is not conclusive, lycopene in tomato products may reduce the risk of prostate cancer.
- Although the evidence is not conclusive, lycopene in tomatoes and tomato products may reduce the risk of prostate cancer.
- Although the evidence is not conclusive, lycopene in tomato products may reduce the risk of prostate cancer when consumed as part of a healthy diet.
- Although the evidence is not conclusive, lycopene in tomatoes and tomato products may reduce the risk of prostate cancer when consumed as part of a healthy diet.
- Although the evidence is not conclusive, lycopene in fruits and vegetables, including tomatoes and tomato products, may reduce the risk of prostate cancer.

NOTES

The following article was not obtained:

Baldwin, D, Naco, G, Petersen, F, Fraser, G, and Ruckle, H. "The effect of nutritional and clinical factors upon serum prostate-specific antigen and prostate cancer in a population of elderly California men **(abstract)**." *Annual Meeting of the American Urological Association* 1997.

No library was able to supply this item, and all other possible sources were exhausted.

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