Tomatoes, Lycopene, and Prostate Cancer

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Several recent publications have established the hypothesis that the consumption of tomato products is associated with a reduced risk of prostate cancer. Lycopene, the carotenoid providing the rich red color of tomatoes, has been identified as one key component of tomato products that may have anticancer properties. However, it is premature to suggest that either tomatoes or lycopene is causally related to protection from prostate cancer or that the consumption of products rich in lycopene will have a beneficial effect for men suffering from established prostate cancer. In order for nutritional scientists, cancer biologists, and epidemiologists to test these hypotheses, it is important to consider how the consumption of tomato products or lycopene may integrate within our current understanding of the prostate cancer cascade. This review will provide an introduction to the etiology and pathogenesis of prostate cancer with an emphasis upon the recent data concerning tomatoes and lycopene.

Prostate cancer has emerged as an increasingly important health problem for American men. Over 200,000 new cases will be diagnosed and over 40,000 men will die of prostate cancer in the United States during 1997 (1). The number of diagnosed prostate cancers in the United States has been gradually rising over the last several decades but has increased dramatically since 1988 when PSA screening became commonplace. Prostate cancer is primarily a disease of older men and is rare prior to the age of 40. Prostate cancer exhibits one of the steepest age-specific incidence curves observed. African-American men have a greater risk than Caucasians or other ethnic groups living in the United States, and overall have one of the highest rates of prostate cancer in the world. Adjustment for socioeconomic and educational experience has not accounted for the greater incidence observed in African-American men. The underlying causes of the racial differences in risk remain speculative.

At least a 30-fold difference in prostate cancer risk is observed between nations having the very lowest rates such as China and Japan and those nations exhibiting the highest risk of prostate cancer such as the economically developed nations of North America, western and northern Europe, and Australia (Fig. 1) (1). An increase in prostate cancer risk is appreciated in migrants to the United States from areas of the world having lower prevalence of this disease suggesting an important role for environmental and lifestyle factors in prostate cancer risk (2, 3).

Pathogenesis of Prostate Cancer

The stepwise process whereby the normal prostatic epithelium progresses to invasive prostate cancer is beginning to be understood although significant gaps in our knowledge remain. Understanding the pathogenesis of prostate cancer and identifying histopathologic markers of progression are critically important for nutritional scientists interested in halting the progression of the disease with tomato products, lycopene, or other dietary interventions. Future investigators will focus their attention upon altering the incidence or progression of premalignant lesions characterized by histologic criteria in younger men at high risk.

The identification and characterization of histologic precursors of prostate cancer remains controversial (4). Pathologists are beginning to agree on a classification of atypical proliferative lesions that may be precursors to cancer. Prostatic intraepithelial neoplasia (PIN) is a lesion of the epithelium of ducts and acini characterized by architectural and cytological abnormalities (5). An additional lesion, characterized by the formation of new ductal and acinar units with minimal cytological atypia is referred to as atypical adenomatous hyperplasia (AAH) or adenosis (6). The relationship between PIN and cancer is more firmly established than the role for AAH (5, 7). The term "latent" prostate cancer is frequently used to define lesions that are cancers by histologic criteria but discovered only on postmortem evaluation. Many readers mistakenly assume that these lesions have low virulence, but the biologic potential of each lesion to progress cannot be ascertained by any current criteria applied in autopsy samples.

The development of clinically significant prostate cancer probably requires decades in the majority of men, although rates of progression most likely vary widely. The observation that PIN and latent prostate cancer can be detected at high frequency in the prostates of young men supports the concept of a very long period of progression from the first histologic abnormalities to the time of diagnosis. For example, autopsy studies show that latent tumors be-

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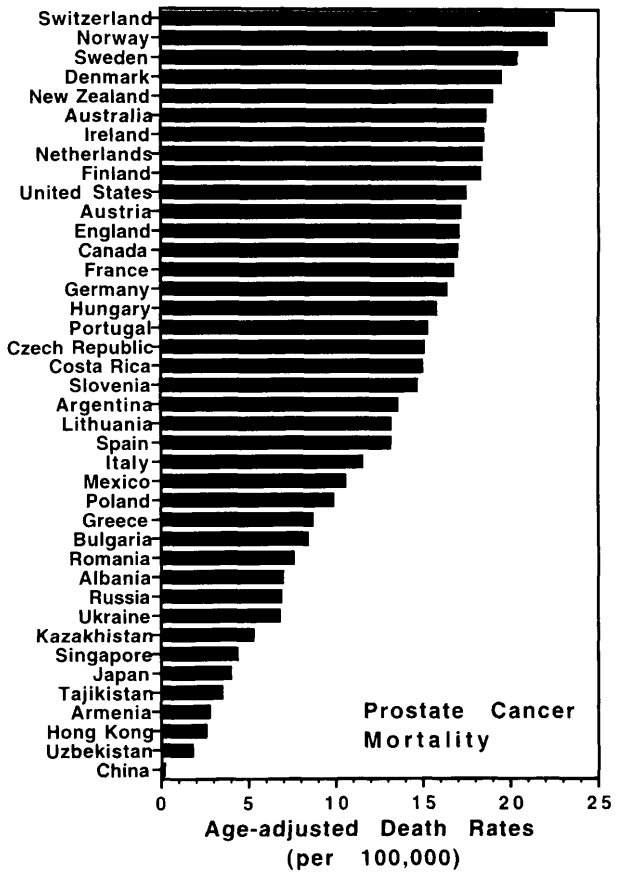

Figure 1. Age-adjusted death rates from prostate cancer per 100,000 population in various nations around the world (1).

come detectable around the age of 30 and then become increasingly more frequent with aging (8–10). Indeed, 70%–90% of mean at the age of 80–90 years may have histologic evidence of prostate cancer at autopsy (4, 11). Similarly, PIN can be detected with considerable frequency in men beginning after age 20 with a continued increase with aging (4, 10, 12). Of considerable interest is the observation that the prevalence of latent prostate cancer in autopsy studies is very similar among geographic areas of the world that exhibit quite different rates of prostate cancer mortality (4). These observations suggest that a critical determinant of prostate cancer incidence and mortality is the progression from latent forms to tumors having more aggressive biology. The possibility that diet and nutrition play a prominent role in accelerating or inhibiting this process is strong.

Once a man has been diagnosed with prostate cancer, the risk of developing metastatic disease or dying of the disease is related to several factors. A significant proportion of men treated for prostate cancer will die of other causes, due to the fact that prostate cancer is a slowly progressive disease in many men, and numerous types of competing mortality exist in the aging male population. However, we can conclude that younger age, higher tumor grade, and advanced stage at the time of diagnosis are associated with very high prostate cancer–specific mortality (13). Indeed, once disease is detected at metastatic sites, the time to progression after beginning hormonal therapy averages 12–24 months. Survival after failure of initial endocrine therapy is typically another 12–24 months. Although some investigators may attempt to alter the progression of hormone-refractory prostate cancer by nutritional intervention, the possibility of success is limited. However, the subgroups of men with rising PSA after primary therapy or those who have chosen observation alone provide opportunities to assess the power of dietary interventions to alter the progression of established disease using biomarkers as surrogate endpoints.

Genetic and Environmental Risk Factors

The evaluation of family history has identified inheritance patterns as one contributor to prostate cancer risk (4, 14). For example, the relative risk is increased 2- to 3-fold for men having a first degree relative with prostate cancer compared to those with no affected relatives. However, the vast majority of prostate cancer occurs in men without a family history. Investigators are only beginning to identify specific genes related to prostate cancer risk (4, 14–16). It is probable that many, yet to be identified, genetic polymorphisms modulating hormone secretion and action as well as nutrient absorption, distribution, and metabolism may contribute to risk. Occupational exposures probably do not account for an appreciable proportion of prostate cancer although workers in heavy industry, newspaper printing, farming, rubber manufacturing, and exposures to cadmium have received considerable study (4, 17–19). The association between tobacco and prostate cancer has been inconsistent (20, 21). However, several studies have reported higher incidence and mortality rates from prostate cancer among smokers (22–26). Preliminary data from the Health Professionals Follow-Up Study shows that smoking in the recent years prior to diagnosis is related to more aggressive and lethal prostate cancer (Giovannucci *et al.*, preliminary data). Men reporting a higher frequency of intercourse, greater number of sexual partners, and past history of venereal disease may experience an increased risk of prostate cancer (4). A modest association between vasectomy and higher risk of prostate cancer has been detected in some studies although mechanisms remain to be identified, and results have not been consistent (4, 27). A better understanding of the genetic and environmental exposures associated with prostate cancer will allow nutritional scientists the opportunity to select motivated subgroups for intervention studies that have a greater likelihood of exhibiting outcomes of interest, thereby reducing costs.

Hormones and Prostate Cancer

The embryological development, growth, differentiation, and function of the prostate gland is controlled by a

complex and integrative network of hormones. Although androgens are the most critical, other hormones such as prolactin, growth hormone, insulin and insulin-like growth factors, thyroid hormones, adrenal hormones, and estrogens all influence prostate biology. The hypothesis that serum concentrations of androgens and other hormones may be correlated to risk of prostate cancer has been investigated in many studies (4, 20, 28–33). Overall, the results of most case-control studies have been uninformative, due to the limited size and power of most studies and the failure to control for factors related to circulating hormone concentrations, such as weight, age, smoking, alcohol, diet, and medications (34). In addition, case-control studies can be compromised by the effects of active prostate cancer or its treatment on hormone profiles. Although prospective serological studies may overcome some of the methodological problems, few have been completed thus far. A recent study reported a significant trend of increasing prostate cancer risk with greater concentrations of plasma testosterone (35). Overall, it is very clear that hormone profiles and receptor activity contribute to prostate cancer progression. However, much more work is necessary to understand how hormone synthesis, metabolism, and bioactivity may ultimately interact with dietary components and nutrition to modulate risk.

Diet and Nutrition

Although a causal relationship for any specific dietary factor and prostate cancer risk remains to be defined, a number of hypotheses are being investigated (36–39). In general, prostate cancer is common in nations with an affluent dietary pattern characterized by surplus energy, high-fat concentrations, excessive saturated fats, and highly refined carbohydrates, whereas the proportion of the diet derived from fruits, vegetables, and whole grain products is low. A detailed review of the major nutritional hypotheses is beyond the scope of this review (36, 37, 40). Thus far it has not been possible to disentangle the interrelationships between energy intake, anthropometrics, physical activity, and the many genetic and environmental variables that modulate these factors and define their roles in prostate carcinogenesis; much more investigation is necessary (38). In general, many of the epidemiologic studies and those in rodent models suggest that a diet rich in total fat and particularly saturated fats is associated with greater risk or enhanced progression of prostate cancer (36, 41–49). Very limited data are available concerning the relationship of total protein or animal versus vegetable protein and the risk of prostate cancer. Positive associations have been suggested in a few human studies (41, 50). We have observed that a diet restricted in protein and energy is associated with reduced growth of rat prostate tumors together with reduced concentrations of serum androgens, growth hormone, and prolactin, as well as reduced prostate prolactin receptor density (51). Among food groups, a correlation is frequently reported between diets rich in meat or dairy products and prostate cancer risk, and these relationships continue to be the focus of additional investigation; mechanisms remain to be defined (22, 41, 43, 49, 50, 52–59).

There are very few evidence-based hypotheses concerning the role of vitamins and minerals in prostate cancer. Of interest, vitamin E and prostate cancer risk were examined in a recent interventional trial conducted in Finland among men at high risk of lung cancer. A significant inverse association between vitamin E supplementation and risk of prostate cancer was observed over several years of follow-up (60). An adequate intake of vitamin A or retinol is necessary for the normal growth and physiologic function of the prostate (61, 62). Studies have reported the presence of retinol binding proteins and receptors in prostate cells (63–65), interactive effects between vitamin A and hormones (66, 67), and the ability of synthetic retinoids to modulate prostate tumorigenesis (68–70). However, most of the epidemiologic data concerning vitamin A intake and prostate cancer risk are inconsistent and preclude making any specific dietary recommendations (36, 71). Selenium has recently received attention based upon a study designed to examine the effects of selenium supplements on skin cancer. Although no effect on skin cancer was observed, supplemented men had a significant reduction in total cancer mortality and a lower incidence of prostate cancer (72). The calcium, phosphorus, and vitamin D network illustrates a complex interaction between dietary intake, endocrinology, and genetics with regard to prostate cancer risk. At this time it is not possible to formulate a unifying hypothesis regarding the accumulated data suggesting that these factors may modulate prostate cancer risk. Some studies report that men who had high $1,25(OH)_2$-vitamin D simultaneously with low 25(OH)-vitamin D levels are at lowest risk of developing prostate cancer (73, 74). In particular, risk of anaplastic and palpable tumors was remarkably low in these studies when levels of $1,25(OH)_2$-vitamin D were high. Prostate epithelial cells possess vitamin D receptors, and $1,25(OH)_2$-vitamin D induces differentiation and modulates proliferation of prostate cells in culture (75–79), whereas newly developed analogs of vitamin D possess a modest ability to alter the growth of prostate carcinoma in rodents (80, 81). Two studies, currently under review for publication, have investigated the role of dietary and supplementary calcium on risk of prostate cancer. Both studies, one from Sweden and the other from the United States, collected dietary intake and reported that the consumption of calcium from dairy or nondairy sources including supplements is associated with an increased risk of aggressive prostate cancer.

These, as well as many new hypotheses will be evaluated in ongoing and future studies as the number of investigators focusing upon prostate cancer continues to expand. Overall, the long latency of prostate cancer provides many opportunities during the life cycle where diet and nutrition may modulate risk. The possibility that dietary interventions

may reduce risk or even slow the rate of progression is a realistic goal for investigators. Furthermore, as we learn more about the roles that specific dietary components play in the prostate cancer cascade, we will also establish opportunities for the development of chemopreventive agents based upon pharmacologic preparations of nutrients and phytochemicals.

Tomato Products and Prostate Cancer Risk

Experimental Approaches and Techniques.

The hypothesis that tomato products or lycopene may have properties that inhibit prostate carcinogenesis evolved from several epidemiologic studies and has now been extended to clinical and laboratory investigations. Two general types of study designs have been used by epidemiologists to examine consumption of lycopene or tomato products in relation to risk of prostate cancer. One approach is based on a dietary questionnaire to assess directly the consumption frequency of various tomato products. These data can then be employed to estimate lycopene consumption using the recently published carotenoid composition of foods typically consumed in the United States (82). Many studies in the literature prior to availability of the carotenoid data base examined food items or food groups that are rich in specific carotenoids, such as lycopene. For example, in the United States and most countries, tomatoes and tomato-based products provide the major proportion of dietary lycopene and can be used as a surrogate indicator of total lycopene intake. The second epidemiologic approach is based on measuring concentrations of carotenoids in stored blood samples as part of case-control investigations or prospective studies. While it is not possible to show definitely that tomatoes or lycopene consumption would reduce risk of prostate cancer based on these types of data, carefully conducted studies would help establish a confidence index, as well as provide a rationale for additional research efforts.

Several clinical investigators are beginning to examine lycopene distribution to the prostate and its relationship to serum carotenoid profiles and dietary intake. The assessment of lycopene in the prostate and its quantitative relationship to biomarkers of progression such as tumor grade, stage, morphometrics, ploidy, mutational patterns, expression of growth factors, or measures of oxidative damage will be very valuable in generating hypotheses concerning mechanisms of action. Thus far, a single report has evaluated lycopene concentrations in the human prostate (Fig. 2) (83).

Rodent models have been very useful for assessing many diet and cancer hypotheses under precisely controlled conditions (37, 84). Although the selection of rodent experimental models for prostate cancer is very limited, several have been employed in nutritional investigations (47, 51, 85). Very little is known about the absorption and distribution of dietary lycopene in rodents and its effects on tumorigenesis. Preliminary studies in our laboratory with lycopene provided from oleoresin (lipid concentrate), tomato powder, and other vehicles suggest that rats and mice absorb lycopene poorly from semipurified diets. However, if the concentrations of lycopene in the rodent diet are increased to concentrations higher than found in human diets, we can achieve tissue concentrations in rodents that are similar to those reported for humans. The diets must be prepared carefully with minimal heat during mixing and pelleting and no light exposure to insure the stability of lycopene. In addition, we freeze the diets, store them in the dark, and provide food daily to avoid degradation prior to consumption. All investigators should carefully monitor food intake and body weight in all rodent nutrition and cancer studies since energy intake is a profound stimulus for tumor growth (37, 86). We recommend that investigators quantitate by HPLC the actual concentration and the isomer pattern of lycopene present after diet preparation. Our preliminary studies suggest an increase in *cis* isomers of lycopene in the diet after formulation. Differences in absorption and biological action between *cis* or *trans* isomers have been hypothesized but have not been tested yet in experimental systems. In addition, it is critical that investigators determine blood and tissue concentrations of lycopene over time in order to interpret the study results and place the data in perspective relative to concentration observed in humans.

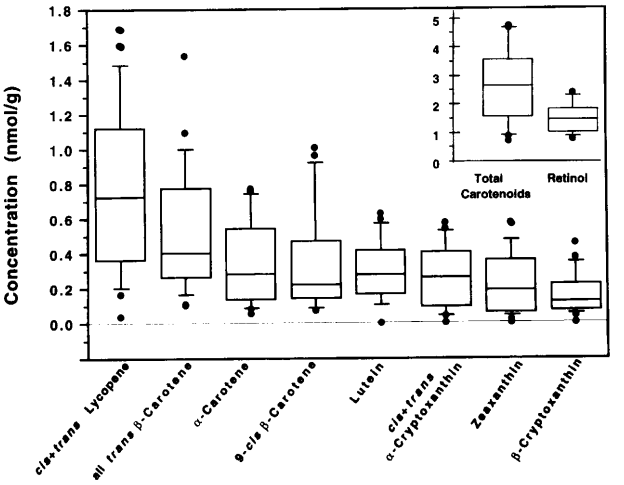

Figure 2. The concentrations of individual carotenoids and vitamin A were measured in human prostate tissue for 25 men undergoing prostatectomy for localized prostate cancer (83). The data is presented as box plots showing the 10th and 90th percentiles (ends of the whiskers), the 25th and 75th percentiles (ends of the box), and the 50th percentile (line within the box). Any outlier points are depicted as individual values.

Cell culture systems provide the opportunity to investigate molecular and biochemical roles for lycopene in a homogeneous population of prostate cells. In general, the cell lines commonly used were established from metastatic prostate cancer and exhibit features of very aggressive, poorly differentiated tumors. Although some investigators are developing techniques to grow normal cells or tumor cells having more well-differentiated features, these efforts have not yet produced lines that are readily available. Ca-

Table I. Prostate Cancer Risk Relative to Estimated Intake of Specific Carotenoids Based Upon Self-Reported Selection of Fruits and Vegetables by Members of the Health Professional's Follow-Up Study [87]

Variable	Quintile of intake†§					*P* for trend
	1	2	3	4	5	
α-Carotene, μg	<380	380–522	523–722	723–1339	1339	
RR*	1.0	1.05	1.09	1.07	1.09	.77
95%CI	—	0.82–1.33	0.86–1.37	0.85–1.35	0.87–1.36	
β-Carotene, μg	<2809	2809–3901	3902–5189	5190–7325	>7325	
RR*	1.0	1.24	0.96	0.99	1.05	.70
95% CI	—	0.98–1.57	0.75–1.23	0.78–1.26	0.83–1.32	
β-Crypto-xanthin, μg	<22	22–40	41–67	68–114	>114	
RR*	1.0	0.97	1.14	0.99	0.94	.76
95% CI	—	0.77–1.24	0.91–1.42	0.79–1.25	.75–1.117	
Lutein‡, μg	<1799	1799–2665	2666–3620	3621–5100	>5100	
RR*	1.0	1.01	1.01	0.96	1.10	.34
95% CI	—	0.80–1.26	0.81–1.27	0.76–1.21	0.88–1.37	
Lycopene, μg	<2262	2262–3366	3367–4591	4592–6460	>6460	
RR*	1.0	0.90	0.94	0.89	0.79	.04
95% CI	—	0.72–1.12	0.76–1.17	0.72–1.11	0.64–0.99	

* RR of energy-adjusted nutrient, adjusted for age by stratified analysis (Mantel-Haenszel estimate).
† 1 = lowest; 5 = highest.
§ Mean intakes for the lower and upper quintiles were 243 μg and 2211 for α-carotene, 2072 and 10,799 μg for β-carotene, 11 and 194 μg for β-cryptoxanthin, and 10,078 μg for lycopene, and 1233 and 7861 μg for lutein, respectively.
‡ Procedure for food composition analysis used by some investigators did not permit separation of lutein and zeaxanthin. Thus, this variable actually represents lutein and zeaxanthin. However, most of the foods evaluated in the questionnaire contain essentially no zeaxanthin. Therefore, the values primarily represent lutein.

rotenoid research presents several obstacles for cell biologists. The possibility of detecting effects that are artifacts of experimental techniques is very high. Our preliminary studies suggest that lycopene and β-carotene are very unstable over several days of *in vitro* incubation in an oxygen-rich warm environment.[2] Investigators must consider the relative merit of several methods for the incorporation of lycopene into cell culture media. For example, cells may be exposed to lycopene *via* solubilization in organic solvents, water soluble beadlets, artificial liposomes, or enriched bovine serum. Each of these approaches provides differing stability and uptake of carotenoids by the prostate tumor cells in culture. It is critical that investigators working with lycopene in prostate cell culture incorporate HPLC analysis of carotenoid stability, cellular concentrations, and metabolism into their investigations.

Studies Based on Dietary Data. Two prospective studies report data on the relationship between tomato consumption and prostate cancer risk. One of these studies was conducted in a cohort of 14,000 Seventh-Day Adventist men, a religious group consuming lacto-ovo vegetarian diets and therefore diets low in meat (56). Men completed a dietary questionnaire in 1976 and were monitored for cancer incidence through 1982. During the 6 years of follow-up, 180 histologically confirmed prostate cancers were detected. The dietary instrument was designed to examine certain food groups rather than nutrient intake. In a multivariate analysis, only tomato intake and consumption of beans, lentils, and peas were significantly related to lower prostate cancer risk. Specifically, the consumption of tomatoes from 1–4 times per week, compared to <1 serving per week, was associated with a relative risk (RR) of 0.64 (confidence interval (CI), 0.42–0.97). Furthermore, a consumption frequency of ⩾5 times per week was associated with a RR of 0.60 (CI, 0.37–0.97). These relationships were independent of other dietary factors including β-carotene-rich foods.

The largest and most comprehensive study completed thus far was based upon data from the Health Professionals Follow-Up Study, a large cohort of U.S. male health professionals (87). Dietary intake was assessed using a validated 131-item food frequency questionnaire in 47,894 health professionals initially free of cancer in 1986. Based on the specific carotenoid content of foods (82) and the self-reported intakes of fruits and vegetables, estimated individual intakes for β-carotene, α-carotene, lutein, β-cryptoxanthin and lycopene were calculated. Between 1986 and 1992, 812 new cases of prostate cancer were diagnosed in these men. Estimated intake of β-carotene, α-carotene, lutein and β-cryptoxanthin were not associated with risk of prostate cancer in this study. In contrast, greater lycopene

[2] Williams AW, Boileau TW-M, Zhou JR, Clinton SK, Erdman JW Jr. β-carotene and prostate cancer cells *in vitro:* Quantitation of stability and cellular uptake with different delivery methods and evidence for metabolic conversion to retinol. In review.

intake was related to a statistically significant 21% reduction in risk of prostate cancer (Table I).

The specific food items that were the major contributors of the various dietary carotenoids were also assessed in these men. Of 46 vegetables and fruits or related products, four were significantly associated with lower prostate cancer risk; three of the four—tomato sauce, tomatoes and pizza—were the primary contributors of lycopene (Table II). Combined intake of tomatoes and tomato products, which accounted for 82% of estimated lycopene intake, was associated with a 35% lower risk of prostate cancer (for consumption frequency >10 versus <1.5 servings/week). The apparent protective effect was even stronger (RR = 0.47) for the more advanced or aggressive prostate cancers, those more likely to cause death (Table III). Of all 131 items on the questionnaire, tomato sauce had the strongest inverse association with prostate cancer risk (RR = 0.66, 95% CI, 0.49–0.90). In this cohort, another 131-item questionnaire was administered in 1990, and tomato sauce was again the item most strongly related to a lower risk of prostate cancer. Subsequent follow-up during 1991–1993 again revealed that tomato sauce was strongly related to a lower risk of

Table II. Prostate Cancer Risk in the Health Professionals Follow-Up Study According to the Consumption of Foods Rich in Various Carotenoids [87]

Food†	No. of servings*					
	0	1–3/mo	1/wk	2–4/wk	≥5/wk	*P* for trend‡
Carrots§ π						
RR (95% CI)	1.0	1.18 (0.87–1.60)	1.22 (0.90–1.65)	1.14 (0.84–1.56)	1.06 (0.71–1.58)	.54
Yams or sweet potatoes§						
RR (95% CI)	1.0	0.93 (0.80–1.09)	0.86 (0.66–1.11)	0.83 (0.56–1.23)		.18
Mixed vegetables						
RR (95% CI)	1.0	0.94 (0.78–1.13)	0.97 (0.80–1.19)	0.96 (0.75–1.21)		.68
Spinach, cooked§,¶						
RR (95% CI)	1.0	1.00 (0.85–1.17)	0.97 (0.78–1.21)	1.22 (0.88–1.9)		.51
Spinach, raw§,¶						
RR (95% CI)	1.0	0.96 (0.81–1.13)	1.07 (0.82–1.82)	1.31 (0.90–1.90)		.34
Canteloupe§						
RR (95% CI)	1.0	1.02 (0.86–1.22)	0.87 (0.70–1.08)	0.98 (0.75–1.27)		.35
Broccoli¶						
RR (95% CI)	1.0	0.96 (0.77–1.20)	0.76 (0.60–0.96)	1.05 (0.83–1.34)		.17
Kale, mustard, or chard¶						
RR (95% CI)	1.0	1.04 (0.82–1.33)	1.09 (0.78–1.51)			
Orange#						
RR (95% CI)	1.0	0.91 (0.73–1.14)	0.97 (0.76–1.24)	0.99 (0.79–1.24)	0.94 (0.72–1.22)	.80
Tomato sauce**						
RR (95% CI)	1.0	0.85 (0.71–1.02)	0.77 (0.62–0.95)	0.66 (0.49–0.90)		.001
Tomatoes**						
RR (95% CI)	1.0	0.90 (0.72–1.13)	0.91 (0.75–1.11)	0.74 (0.58–0.93)		.03
Pizza**						
RR (95% CI)	1.0	0.94 (0.80–1.10)	0.76 (0.57–1.01)	0.85 (0.45–1.58)		.05
Tomato Juice**						
RR (95% CI)	1.0	1.02 (0.86–1.21)	0.85 (0.65–1.11)	1.15 (0.90–1.49)		.67

* Categories determined a priority on the basis of ranges of intake. Upper category for each item includes all higher-intake levels up to six serving per day.
† No. of cases does not always total 773 because some did not respond for specific food items.
‡ Test for trend determined by Mantel extension test.
§ Primary contributor of β-carotene.
π Primary contributor of α-carotene
¶ Primary contributor of lutein.
# Primary contributor of β-cryptoxanthin.
** Primary contributor of lycopene.

prostate cancer (unpublished data). Inverse associations observed with tomatoes and pizza were weaker, and no relationship was observed between tomato juice and prostate cancer risk.

The finding that tomato sauce was the major predictor of lower prostate cancer risk, whereas tomato juice was uncorrelated with risk is interesting in light of previous work suggesting that lycopene in tomato juice is not efficiently absorbed unless the juice is heated in an oil-based medium (88). The authors of that report hypothesized that absorption from the intestine is facilitated by the thermally induced rupture of cell walls, dissolution of the lycopene from the cell matrix, and enhanced solubilization of lycopene into the oily medium. The correlation between dietary sources of lycopene and plasma concentrations was explored further in an analysis of a subset of 121 Health Professionals Follow-Up Study cohort members who provided blood samples. Tomato sauce, which is usually cooked and consumed with lipids, was the major predictor of plasma lycopene levels (Pearson correlation $r = 0.34$; $P = 0.0001$), followed by tomatoes ($r = 0.17$; $P = 0.056$), whereas tomato juice was uncorrelated with plasma levels ($r = -0.10$; $P = 0.28$). These observations suggest that the relatively low bioavailability of lycopene could account, at least in part, for the lack of association between reported tomato juice intake and prostate cancer risk. If bioavailability of a nutrient varies markedly across food items, an alternative to the calculation of nutrient intakes using the published values is to employ empirically derived weights for each food item to predict a biomarker of intake. This empirical approach has the advantage that it avoids many assumptions regarding validity of responses to a particular item, portion sizes, nutrient composition, and bioavailability. Thus, an empirical score was calculated using a stepwise linear regression model of lycopene-containing foods to predict plasma lycopene levels in the subsample of 121 men. Each cohort member then received an empirical score based on the derived weights. The lycopene score was a strong predictor of reduced prostate cancer risk (RR = 0.72, CI, 0.57–0.91, for the highest versus the lowest quintiles; *P,* trend, = 0.01) and advanced stage (stage C or D, or fatal) prostate cancer (RR = 0.57, CI, 0.37–0.87; *P,* trend, = 0.02).

Two other studies have addressed the tomato and prostate cancer relationship. A case-control study conducted in Minnesota found a nonsignificant inverse association between tomato intake and risk of prostate cancer (89). Another case-control study of 452 prostate cancer cases and 899 population controls conducted in a multiethnic population in Hawaii (90) reported no association with consumption of "tomatoes." However, the intake levels were not indicated, and it did not appear that tomato-based products such as tomato sauce were specifically addressed.

Studies Based on Stored Sera. Two studies have examined serum lycopene and other carotenoids, using prediagnostic samples, in relation to prostate cancer risk. The first study was based on serum obtained in 1974 from 25,802 persons in Washington county (91). Serum levels of the nutrients in 103 men who developed prostate cancer during the subsequent 13 years of follow-up were compared with levels in 103 control subjects matched for age and race. The investigators found a 6.2% lower median lycopene level in men subsequently developing prostate cancer compared to controls. The estimated relative risk was 0.50 (CI, 0.20–1.29) between high and low quartiles of blood lycopene. The RR was stronger (RR = 0.35) among men under the age of 70. However, because the study was very small with only 103 case-control pairs, these associations were not statistically significant. No other carotenoid exhibited any trends relative to prostate cancer risk.

The second sera-based study was conducted in a Japanese-American population in Hawaii between 1971 and 1993 (92). In this cohort of 6860 men, a single blood specimen was collected in 1971 to 1975. Up to 1993, 142 tissue-confirmed incident cases of prostate cancer were identified. The prediagnostic serum levels in the cases were compared with those of 142 matched controls. This study did not detect any association between serum lycopene concentrations and risk of prostate cancer. However, several characteristics of the study may have contributed to the null association. The evaluation was based on a single assessment of serum lycopene, which was used to characterize follow-up for up to a 22-year period. Secondly, 28% of the cases were diagnosed incidentally during surgery for benign prostatic hypertrophy, and only 14 of the cases occurred within the first 5 years of follow-up following collection of the single blood sample. In the Health Professionals Follow-Up Study, inverse associations with lycopene were considerably stronger for more aggressive cancers and for more recent tomato product consumption (for example, 1990 intake predicted 1990–1991 risk of prostate cancer considerably better than did the 1986 diet). Most importantly, the serum lycopene concentrations were very low compared to other populations. The median serum concentration among controls was only 134 ng/ml compared to 320 ng/ml in the Hsing *et al.* study (91) and 424 ng/ml in the sample of 121 health professionals. Ethnic differences may also be important as the Japanese in Hawaii had about half the incidence rate of prostate cancer as Caucasians in Hawaii.

Studies of Human Prostate Tissue. If lycopene contributes to a lower risk of prostate cancer, the mechanisms remain speculative. Perhaps lycopene acts within the host to alter hormone status or immune function in a manner that inhibits the progression of prostate cancer. However, we speculate that lycopene may have a direct effect on the prostate. If lycopene directly influences prostate gland biology, we proposed that lycopene should be detectable within the prostate. We completed a study to determine the patterns and concentrations of carotenoids and lycopene isomers in human prostate tissue ($n = 25$) (83). A diverse array of carotenoids was observed, which generally reflects consumption patterns in American men (Fig. 2). Lyco-

pene was found at the highest concentration in 64% of the prostates evaluated. The range of lycopene observed in human prostate tissue extended from the undetectable range to 1.8 n*M*/g, and total carotenoids within the prostate ranged from 0.75 to 5 n*M*/g. The proportion of lycopene distributed among all-*trans* versus *cis*-isomers varies significantly between food products, human serum, and prostate tissue. All-*trans* lycopene is predominant in tomatoes and tomato-based foods accounting for 80%–90% of total lycopene with the remainder distributed among several small *cis*-isomer peaks. In contrast, all-*trans* lycopene accounts for only 10%–25% and *cis*-isomers for 75%–90% of total lycopene in prostate tissue. The *cis*-isomers were distributed among 14–18 peaks in human prostate tissue and 12–13 peaks in serum. Serum all-*trans* lycopene averaged about 40% while *cis*-isomers accounted for approximately 60%. What biological factors account for the increased proportion of *cis*-isomers in serum and prostate tissue compared to the diet remain to be defined. Most importantly, the specific molecular and biological functions (if any) of specific isomers remain unknown and the focus of ongoing studies.

Summary

The epidemiologic data tend to support an association between intake of tomato-based foods and a lower risk of prostate cancer. The observed inverse association may be due to lycopene though this is unproven at this point. Even two servings a week of a rich source of bioavailable lycopene, such as tomato sauce, was related to a substantially lower risk of prostate cancer. Whereas chance alone is highly unlikely to account for the consistent inverse association with tomato-based products, confounding by other variables, particularly dietary, cannot be definitively excluded as alternative explanations. Of greatest concern is that a lycopene-rich diet is acting as an indicator of a diet rich in vegetables and fruits that may lower risk of prostate cancer through other phytochemicals. An important historical lesson is provided by β-carotene, for which an abundance of evidence based on questionnaires and blood levels suggested a benefit on various cancers (93), particularly lung cancer, but recent intervention trials of β-carotene supplementation have not confirmed this benefit (60). In retrospect it appears difficult, if not impossible to differentiate β-carotene intake from that of a general dietary pattern that is high in fruits and vegetables. In contrast, this is not the case for lycopene. Other carotenoids in prostate tissue tend to be significantly interrelated, but lycopene content does not appear to be correlated appreciably with other carotenoids (83). In the Health Professionals Follow-Up Study and the Seventh-Day Adventist study, tomato-based products and lycopene were associated with a lower prostate cancer risk, but fruits and vegetables, individually and in aggregate, and other carotenoids were not associated with prostate cancer risk. These results are consistent with findings from other studies that overall vegetable and fruit consumption appear unrelated to prostate cancer incidence (36, 94, 95). It is more difficult to separate specific effects of lycopene from that of other potentially beneficial compounds in tomatoes; however, based on similarity of results for plasma predictors of lycopene with predictors of prostate cancer risk, the putative compound would be expected to have similar bioavailability characteristics as lycopene. Thus, with regard to practical recommendations, the available data are most conservatively interpreted as supporting a potential benefit of increased consumption of tomatoes and tomato-based products. To attribute a specific effect to lycopene or a particular isomer of this carotenoid would require much more research. Additional studies by epidemiologists, clinical investigators, cancer biologists, and nutritional scientists are underway, and answers to many questions concerning tomatoes, lycopene, and prostate cancer should be forthcoming.

Table III. The Risk of Prostate Cancer of Higher Stage Based Upon the Number of Servings of Tomato Products per Week [87]

	Tomato-based products, no. of servings per week					
	<1.5	1.5–4.0	4.1–7.0	7.1–10.0	>10	*P* for trend*
Total						
RR	1.0	0.92	0.78	0.85	0.65	.01
95% CI		(0.76–1.12)	(0.63–0.98)	(0.65–1.10)	(0.44–0.95)	
Stage C or D cases						
RR	1.0	1.15	0.86	0.88	0.47	.03
95% CI		(0.83–1.60)	(0.59–1.26)	(0.57–1.38)	(0.22–1.00)	
Stage D cases						
RR	1.0	1.11	0.96	0.94	0.24	.12
95% CI		(0.69–1.78)	(0.57–1.62)	(0.51–1.74)	(0.06–1.02)	

* Test for trend determined by modeling category of intake as an ordinal variable in a regression model.
† Relative risk (RR) adjusted for age and total energy intake by stratified analysis (Mantel-Haenszel estimate).
‡ RR and 95% confidence interval (CI) controlling for age, total energy intake, ancestry, vasectomy status, and intake of animal fat and retinol by proportional hazards regression.

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