A Review of Epidemiologic Studies of Tomatoes, Lycopene, and Prostate Cancer

EDWARD GIOVANNUCCI[1]

Channing Laboratory, Department of Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115; and Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115

Prostate cancer is the most common cancer in American men. Preventable measures for this malignancy are not well established. Among potentially beneficial natural compounds is the carotenoid lycopene, which is derived largely from tomato-based products. Recent epidemiologic studies have suggested a potential benefit of this carotenoid against the risk of prostate cancer, particularly the more lethal forms of this cancer. Five studies support a 30% to 40% reduction in risk associated with high tomato or lycopene consumption, three are consistent with a 30% reduction in risk, but the results were not statistically significant, and seven were not supportive of an association. The largest relevant dietary study, a prospective study in male health professionals found that consumption of two to four servings of tomato sauce per week was associated with about a 35% risk reduction of total prostate cancer and a 50% reduction of advanced (extraprostatic) prostate cancer. Tomato sauce was by far the strongest predictor of plasma lycopene levels in this study. In the largest plasma-based study, very similar risk reductions were observed for total and advanced prostate cancer for the highest versus lowest quintile of lycopene. Other studies, mostly dietary case-control studies, have not been as supportive of this hypothesis. The reasons for these inconsistencies are unclear, but in three of the seven null studies, tomato consumption or serum lycopene level may have been too low to observe an effect. Because the concentration and bioavailability of lycopene vary greatly across the various food items, dietary questionnaires vary markedly in their usefulness of estimating the true variation in tissue lycopene concentrations across individuals. To optimize the interpretation of future findings, the usefulness of the questionnaire to measure lycopene levels in a population should be directly assessed. Although not definitive, the available data suggest that increased consumption of tomatoes and tomato-based products may be prudent. Exp Biol Med 227:852–859, 2002

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Prostate cancer is the most common noncutaneous cancer diagnosed in American men, and is the second leading cause of death from malignancies. The more compelling risk factors for the occurrence or progression of prostate cancer are nonmodifiable; these include older age, a family history of prostate cancer, and race. Other likely risk factors, including the concentrations of various hormones, are not feasibly modifiable. Much interest recently has centered on nutritional or other environmental factors. Some features of a "Western" diet high in red meat and dairy products appears to increase risk of prostate cancer, and some micronutrients, such as selenium and vitamin E, may have potential protective influences. Recently, tomatoes and tomato-based products, the major source of many of the dietary carotenoids including lycopene, have shown promise for the prevention of prostate cancer. The potential impact of tomatoes and lycopene on prostate cancer risk is the focus of this review.

Assessment of Lycopene Intake in Epidemiologic Studies

Carotenoids are a group of at least 600 compounds manufactured by plants, and they account for many of the bright colors in the plant kingdom. Only about 14 carotenoids are found in appreciable levels in human tissues (1). The most common carotenoids in the human diet and plasma are β-carotene, α-carotene, lycopene, lutein, and β-cryptoxanthin. Carotenoids have many interesting properties in biological systems. β-Carotene and a few other carotenoids can be converted to vitamin A. Additionally, carotenoids react with free radicals and singlet oxygen generated by normal cellular respiration and possibly by exogenous sources such as cigarette smoking (2). Of the 14 carotenoids found in human serum, tomato and tomato products contribute to nine and are the predominant source of about one-half, including lycopene. In fact, in most populations particularly in the West, dietary lycopene is supplied largely by tomatoes and tomato-based products. Watermelon and pink grapefruit contribute a relatively small proportion of lycopene as well.

The antioxidant properties of lycopene have stimulated

[1] To whom requests for reprints should be addressed at Channing Laboratory, Department of Medicine Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115. E-mail: Edward.giovannucci@channing.harvard.edu

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an interest in examining this carotenoid, or its major source, tomatoes, in relation to cancers of the prostate gland, as well as other cancer sites (3). However, several factors suggest that substantial variability exists in the effectiveness of various epidemiologic studies to examine this hypothesis. First, a population may consume relatively low levels of lycopene, or there may be insufficient contrast between high and low consumers. Second, the dietary questionnaires may be inadequate in capturing all of the relevant items. For example, many potentially important contributors of lycopene, such as ketchup, tomato soups, tomato sauce, pizza, and salsa (4), are often not considered. Third, there may be inconsistencies in how study participants may interpret questions; for example, the tomato sauce from pizza may not be considered in a single variable "tomato sauce," and items termed "cooked tomatoes" are open to interpretation. Finally, and perhaps most critically, bioavailability of lycopene varies profoundly across specific items. The lycopene in many processed foods such as tomato and spaghetti sauce, tomato soup, salsa, ketchup, and tomato paste are better sources of bioavailable lycopene than are fresh tomatoes (4–6).

That these issues, as well as other potential sources of measurement error, are likely to be of great importance is illustrated in studies that have estimated the correlation between dietary lycopene and plasma or serum lycopene concentrations (7–17). These studies, summarized in Table I, have demonstrated correlations ranging from 0 to 0.47. For men, correlation coefficients have been in the range of 0.2, with the one exception coming from a subgroup in the Health Professionals Follow-Up Study with a correlation coefficient of 0.46. It is unclear why this study yielded such a relatively strong correlation. The questionnaire used was the Willett Food Frequency Questionnaire (FFQ); however, in other populations using the Willett FFQ, correlations have been 0.18 (15) and 0.11 (9). The participants were highly educated health professionals who may have improved response accuracy. In most dietary studies of lycopene and prostate cancer risk, how closely dietary intake reflected circulating or tissue level is not known, but presumably encompassed a similar range as seen in Table I. If so, studies on the lower end in the range of measuring true lycopene intake are likely to be severely compromised in testing the lycopene-prostate cancer hypothesis.

Epidemiologic Studies

A number of epidemiologic studies have correlated risk of prostate cancer with intake of tomatoes and tomato-based products or lycopene. The design of dietary-based studies has been either retrospective (case control), for which prior diet in men with prostate cancer is compared with that of a control or comparison group free of prostate cancer, or prospective, for which diet is measured at baseline and men are followed for prostate cancer occurrence. Case-control studies are summarized in Table II, and prospective studies are considered in Table III. Plasma or serum level studies are summarized in Table IV.

Case-Control Studies. A case-control study of prostate cancer conducted in Minnesota (18) reported that high consumers (>14 times per month) had about a 30% lower risk of total prostate cancer than low consumers (<3 times per month). Another case-control study, conducted in a multiethnic population in Hawaii (19), found no association between consumption of "tomatoes" and prostate cancer risk. However, the actual intakes were not reported, and it did not appear that tomato-based products such as tomato sauce were specifically considered in this study. It is unclear

Table I. Summary of Studies Examining Dietary Intake of Lycopene in Relation to Plasma or Serum Measures

Reference	Composition	Questionanire/database	Diet and plasma (serum) lycopene correlation coefficients		
			Total	Men	Women
7	91 black women	Block HHQ/Block			0.0
8	65 men	Block HHQ/NCI-USDA		0.26	
9	50 men 49 women	Willett FFQ/Minnesota database	0.11		
10,11	58 men (nonsmokers) 56 women (nonsmokers)	Block HHQ Database:			
		Block		0.23	0.37
		NCI-USDA		0.21	0.37
12,13	400 (55% women)	Block HHQ database:			
		Block	0.29		
		NCI-USDA	0.25		
14	91 men 20 women	Block HHQ/Block	0.32		
15	110 men (nonsmokers) 162 women (nonsmokers)	Willett FFQ/NCI-USDA		0.46	0.18
16	47 men	Block HHQ/Block		0.21	
17	931 women	Women's Health Initiative FFQ/NCI-USDA			0.20

Table II. Summary of Diet-Based Case-Control Epidemiologic Studies Examining Tomato Intake or Lycopene Intake or Level and Prostate Cancer

Reference	Place of study	Years of study	Number of cases	Exposure	Relative risk[a] (95% CI)
18	Minnesota	1976–1979	223	Tomato intake, high vs low	0.70 NS
19	Hawaii	1970–1983	452	Lycopene intake	0.9 $P = 0.35$ <70 y
				Quartile 4 vs 1	1.1 $P = 0.57$ ≥70 y
24	United Kingdom	1989–1992	328	Dietary lycopene	0.99 (0.68–1.45)
				≥718 vs <402 μg	$P = 0.88$
				Raw Tomatoes	1.06 (0.55–1.62)
				≥5/week vs ≤3/month	$P = 0.88$
				Cooked tomatoes	0.92 (0.57–1.42)
				≥2/week vs <1/month	$P = 0.64$
				Baked beans[b]	0.52 (0.31–0.88)
				≥2/week vs <1/month	P (trend) = 0.075
25,38	Athens, Greece	1994–1997	320	Raw tomatoes	0.65 (0.40–1.0)
				>30 vs <20/month	P (trend) = 0.12[c]
				Cooked tomatoes	0.52 (0.33–0.83)
				≥28 vs <13/month	P (trend) = 0.005
20	U.S.	1986–1999	449 (black)	Lycopene (combined food sources)	0.9
					P (trend) = 0.07
			483 (white)	≥5/wk vs 0	
26	New Zealand	1996–1997	317	Lycopene	0.76 (0.50–1.17)
				Quintile 4 vs 1	P (trend) = 0.30
				Tomato, tomato-based foods	0.82 (0.53–1.26)
					P (trend) = 0.30
				Raw tomatoes	1.01 (0.66–1.53)
					P (trend) = 0.30
22	U.S. and Canada	1987–1991	1619	>108 g vs <20 g tomatoes/day	1.07 (0.83–1.38)
					P (trend) = 0.85
				>93 g vs ≤18 g cooked tomatoes/day	0.94 (0.58–1.52)
					P (trend) = 0.56
23	Seattle, WA	1993–1996	628	Cooked tomatoes	0.73 (0.48–1.10)
					P (trend) = 0.13
					0.90 (0.57–1.42)
					P (trend) = 0.068
					(adjusted for fruits and vegetables)
				Dietary lycopene	0.89 (0.60–1.31)
				≥9990 μg vs <4900 μg/day	P (trend) = 0.96
27	Canada	1989–1993	617	Tomatoes	
				>73 g vs <24 g/day	0.64 (0.45–0.91)
					P (trend) = 0.02[c]
				Lycopene	
				>12,681 vs <2,103 μg day	0.85 (0.75–0.97)
					P (trend) = 0.005

[a] Relative risk and 95% CI or P for exposure comparison indicated.
[b] Source of highly bioavailable lycopene.
[c] Relative risk not given.

whether the most relevant bioavailable sources of lycopene were assessed in this multiethnic population.

Three recently published case-control studies, also conducted in the United States, have examined dietary lycopene and tomato intake in relation to prostate cancer risk. A study by Hayes *et al.* (20) did not support the lycopene-prostate cancer hypothesis in white or black men. This study did not find statistically significant associations with either total or advanced prostate cancer for various components of tomato products. Some curious findings were that raw, not cooked, tomatoes, had a suggestive inverse association with advanced prostate cancer (relative risk [RR] = 0.5; P [trend] = 0.05), but tomato juice was related to higher risk of prostate cancer for white men (RR = 2.8; P [trend] = 0.02). Of note, tomato juice, possibly because the lycopene is relatively poorly bioavailable, did not correlate with lycopene levels in another population (21).

A large multiethnic case-control study by Kolonel *et al.* (22) did not support an association between raw or cooked tomato intake, or lycopene intake in relation to total or advanced prostate cancer risk. Among black men, there was a suggestion of an inverse association for total prostate cancer for cooked tomatoes (RR = 0.72; 95% CI = 0.41–1.26, between high and low tertiles); even weaker corresponding associations were observed for white men (RR = 0.90; 95% CI = 0.54–1.51) and Japanese men (RR = 0.85; 95% CI =

Table III. Summary of Diet-Based Cohort Epidemiologic Studies Examining Tomato Intake or Lycopene Intake or Level and Prostate Cancer

Reference	Place of study	Years of study	Number of cases	Exposure	Relative risk[a] (95% CI)
28	California Seventh Day Adventists	1974–1982	180	Tomato intake ≥5 vs <1/week	0.60 (0.37–0.97) $P = 0.02$
21	U.S.	1986–1992	773	Dietary tomato based products >10 vs <1.5 servings/week	0.65 (0.44–0.95) $P = 0.01$
				Tomato sauce 2–4 vs 0/week servings/week	0.66 (0.49–0.90) $P = 0.001$
30	Netherlands	1986–1992		Tomatoes (per 25 g increments)	1.05 (0.90–1.22)
29	U.S.	1987–1990	101	Dietary tomatoes Quintile 5 vs 1	0.50 (0.3–0.9) $P = 0.03$

[a] Relative risk and 95% CI or *P*- for exposure comparison indicated; in some cases, measures other than the relative risk were given.

Table IV. Summary of Blood-Based (Cohort) Epidemiologic Studies Examining Tomato Intake or Lycopene Intake or Level and Prostate Cancer

Reference	Place of study	Years of study	Number of cases	Exposure	Relative risk[a] (95% CI)
32	Maryland	1974–1985	103	Serum lycopene Quartile 4 vs 1	0.50 (0.20–1.29) $P = 0.26$
34	Hawaii	1971–1993	142	Serum lycopene Quartile 4 vs 1	1.1 (0.5–2.2) $P = 0.86$
33	U.S.	1982–1995	578	Plasma lycopene >580 vs <262 ng/ml	Total: 0.75 = (0.54–1.06) P (trend) = 0.12 Aggressive: 0.56 (0.34–0.92) P (trend) = 0.05

[a] Relative risk and 95% CI or *P* for exposure comparison indicated.

0.20–3.65). Chinese men, the other ethnic group studied, consumed low amounts of cooked tomato products. One potential limitation of this study was a relatively low response rate among the controls (58%), which possibly may have introduced selection bias.

A recent study conducted in the King County, Seattle area is notable in several regards (23). This study was conducted from 1993 to 1996, when many "prevalent" cancers were first diagnosed, as prostate-specific antigen (PSA) testing was used for the first time for many men. A dramatic increase in prostate cancer diagnoses occurred in the United States during this time period. In addition, the study population was restricted to men under the age of 65, and possibly presenting at an early age may represent an accelerated process of carcinogenesis influenced substantially by genetic factors in ways that are not observed in the majority of cancers presenting at older ages. Neither cooked tomatoes nor tomatoes were appreciably correlated with risk of prostate cancer. Although a suggestive inverse association was noted for cooked tomatoes, RR (adjusted for covariates) = 0.73 (95% CI = 0.48–1.10); P (trend) = 0.13 for ≥3 versus <1 serving per week; this association was largely attenuated when additionally controlled for total fruits or vegetables (RR = 0.90). Although Cohen *et al.* (23) have argued that previous studies that reported an inverse association with tomato products or serum lycopene levels may not have controlled for total fruits and vegetables, fruits and vegetables have not been generally observed to be related to prostate cancer risk or to lycopene levels (9, 15, 17).

Four case-control studies conducted outside the United States were identified. A recent case-control study conducted in the United Kingdom (24) found no association between raw or cooked tomatoes and risk of prostate cancer. However, the strongest diet-prostate cancer association found was for baked beans (RR = 0.52; 95% CI = 0.31–0.88 for high versus low intake). The authors speculated that tinned baked beans, usually stored in tomato sauce, may possibly be the best source of highly bioavailable lycopene in this population. A recent study conducted in Greece (25) found that men with prostate cancer reported slightly less raw tomatoes ($P = 0.12$) but significantly less cooked tomatoes ($P = 0.005$) in their diet. A study in New Zealand (26) found a suggestive but not statistically significant inverse association between total lycopene intake and risk of total prostate cancer (multivariate-adjusted RR = 0.76; 95% CI = 0.50–1.17 between high and low quartiles); to-

mato and tomato-based foods accounted for this suggestive association, but raw tomatoes were not associated with risk. Other carotenoid-rich foods were unrelated to risk. A Canadian case-control study (27) conducted in three regions between 1989 and 1993 did not find an association for total prostate cancer with lycopene intake, but did report a significant inverse association with tomato items. Results separately for advanced prostate cancer were not reported, nor were RRs differentially reported for subclassifications of tomato items (e.g., cooked, processed, and raw).

Prospective Studies. Four dietary prospective studies (21, 28–30) have reported on the relationship between tomato or lycopene consumption and prostate cancer risk (Table III). In a cohort of 14,000 Seventh Day Adventist men (28), higher consumption of tomatoes was statistically significantly related to lower risk of prostate cancer in a multivariate analysis. The only other food item related to a lower prostate cancer risk was intake of beans, lentils, and peas. β-Carotene-rich foods were unrelated to risk.

The largest study to date, conducted in male health professionals (21), was also the only dietary study that had concurrent plasma levels in a sample of participants. As shown in Table I, the correlation between plasma and dietary lycopene ($r = 0.46$) far exceeded that in other populations in which dietary and blood samples were available. Intakes of β-carotene, α-carotene, lutein, and β-cryptoxanthin were not associated with risk of prostate cancer, but high intake of lycopene reduced risk of prostate cancer by 21%. Also, high intake of tomatoes and tomato products, which accounted for 82% of lycopene, was associated with a 35% lower risk of total prostate cancer, and a 53% lower risk of advanced (extraprostatic) prostate cancer. Tomato sauce (2–4 servings/week) had the strongest inverse association with prostate cancer risk (RR = 0.66; 95% CI = 0.49–0.90; P [trend] = 0.001), and weaker inverse associations were observed with tomatoes and pizza, but none with tomato juice. Of note, the degree of reduction of prostate cancer risk by the tomato-related products (tomato sauce, substantial reduction; tomatoes and pizza, moderate reduction; and tomato juice, no reduction) corresponded with the degree that these items correlated with plasma lycopene levels. It is unlikely that another healthy behavior that correlates with tomato intake accounts for the association because tomato products are quite diverse items; some are correlated positively with healthy behaviors (e.g., tomatoes) and some inversely (e.g., pizza), and some (e.g., tomato sauce) display no obvious pattern with healthy behaviors. In an additional analysis based on a dietary empirical score that took bioavailability into account, associations for total lycopene were accentuated (RR [for high versus low quintile] = 0.72; 95% CI = 0.57–0.91 for total prostate cancer; RR = 0.57; 95% CI = 0.37–0.87 for advanced malignancies).

A cohort study conducted in The Netherlands did not report an association between tomato consumption and prostate cancer risk. However, tomato consumption is low in this population and it did not appear that processed or cooked tomato products were explicitly addressed. Preliminary results from another cohort study (29, 31) also support about a 50% reduction in risk in men in the highest quintile of lycopene consumption relative to those in the lowest quintile.

Plasma and Serum-Based Studies. Three studies (32–34) have reported on the risk between prediagnostic serum carotenoids and risk of prostate cancer (Table IV). These studies assessed frozen prediagnostic serum or plasma samples that were collected in large groups of men who subsequently were diagnosed with prostate cancer. Concentrations of carotenoids were then compared with those from a random sample of the men who did not develop prostate cancer in the corresponding time period.

The first published report, a study by Hsing *et al.* (32), was based on serum obtained in 1974 from 25,802 persons in Washington County, Maryland. This study found a 6.2% lower median lycopene level in men with prostate cancer diagnosed during a 13-year period compared with age- and race-matched controls. The relative risk was 0.50 (95% CI = 0.20–1.29) between high and low quartiles of lycopene. Lycopene was the only carotenoid associated with lower prostate cancer risk in this relatively small study.

The largest blood-based study was the Physicians' Health Study (33), a nested case-control study using samples stored in 1982. In total, 578 prostate cancer cases occurred over the 13 years of follow-up. Of the 578 cases, 259 were classified as "aggressive" based on high-grade or advanced stage. The baseline plasma lycopene level of cases was compared with that of age-matched prostate cancer-free controls. The investigators found a lower risk of prostate cancer, particularly for aggressive (high-grade or stage) prostate cancer (RR = 0.56; 95% CI = 0.34–0.92) when comparing high with low quintile of plasma lycopene. None of the other measured carotenoids were related to risk of prostate cancer. As this study population was derived from a randomized trial of β-carotene, analyses were further stratified by β-carotene or placebo assignment; the inverse association with lycopene was largely limited to those who had received placebo rather than β-carotene.

A study of prediagnostic serum carotenoids and prostate cancer risk conducted between 1971 and 1993 in a Japanese-American population in Hawaii (34) did not find an association between serum lycopene levels and risk of prostate cancer. However, several characteristics of the study may have contributed to the null association. Only a single assessment of serum lycopene was used to characterize follow-up for up to a 22-year period (only 14 cases occurred within the first 5 years of follow-up), and the study included "low virulence" prostate cancer (28% were diagnosed incidentally during surgery for benign prostatic hyperplasia) in a low-risk population. These factors might contribute to the null results. Most importantly, the serum lycopene levels were quite low; the median serum concentration among controls was only 134 ng/ml compared with

320 ng/ml in the Hsing *et al.* study (32), 424 ng/ml in the sample of 121 health professionals (21), and 388 ng/ml in the Physicians' Health Study (33). The low levels may indicate very low intake of bioavailable lycopene in this population. In Figure 1, comparisons of the concentrations of various carotenoids in the Japanese-American population and the Physicians' Health Study show quite a different pattern of carotenoids. For example, the ratio of lycopene to β-cryptoxanthin is about 6 in the physicians and about 1 in the Japanese-American men, suggesting quite different dietary patterns.

Synthesis of Current Studies

A number studies have examined tomato product or lycopene intake or circulating lycopene levels in relation to prostate cancer risk. The data are not conclusive at this point, but they suggest that high consumption or high circulating concentrations are associated with a 30%–40% reduction in risk, especially of aggressive prostate cancer. The studies can be summarized as follows: those that support a statistically significant inverse association (21, 25, 28, 29, 33); those consistent with approximately a 30% reduction in risk but that were not statistically significant (18, 26, 32); and those that are nonsupportive (19, 20, 22-24, 30, 34). The results from one study were equivocal, showing a statistically significant inverse association with tomato consumption but not for lycopene intake (27).

As discussed above, there are numerous potential reasons for why an actual association could be missed in a study. It is likely that in some of the nonsupportive studies, intake of tomato products or sources of bioavailable lycopene were too low to be informative. This may have been the case in at least three studies (19, 30, 34). For example, in the serum-based study by Nomura *et al.* (34), the range of lycopene was 3- to 4-fold lower than that in populations for which an association was observed. A clear inverse association was observed only at the highest concentrations of lycopene (>580 ng/ml) in the plasma-based study by Gann *et al.* (33). In the study by Nomura *et al.* (34), although the cutpoint for the high category was not provided, the median level of only 134 ng/ml indicated that not many men attained such high levels in this population.

Four case-control studies provided the strongest evidence against a potential protective effect of lycopene or tomato products. One study was conducted in the United Kingdom, and the others were done in the United States where tomato products intakes are generally high. The British study by Key *et al.* (24) was of interest in showing an inverse association with baked beans, leading the authors to speculate that the tomato paste, which usually accompanies tinned baked beans, may have accounted for this relationship. This explanation, although speculative, is plausible because it is unpredictable what items may best account for true variation in lycopene status in a population. For example, a substudy in the Health Professionals Follow-Up Study indicated that tomato juice, although highly concentrated in lycopene, did not predict plasma lycopene levels because this item was not reported well in this population (15). In addition, the lycopene from this source may have had relatively low bioavailability.

The other null dietary studies apparently had reasonably comprehensive assessments of tomato product intakes, but how well these captured true variation of lycopene in body levels in these populations was not assessed. As discussed above, correlations between reported dietary intakes and circulating levels of lycopene have ranged from 0 to 0.47. The highest reported correlation by far was in the Health Professionals Follow-Up Study, the study population

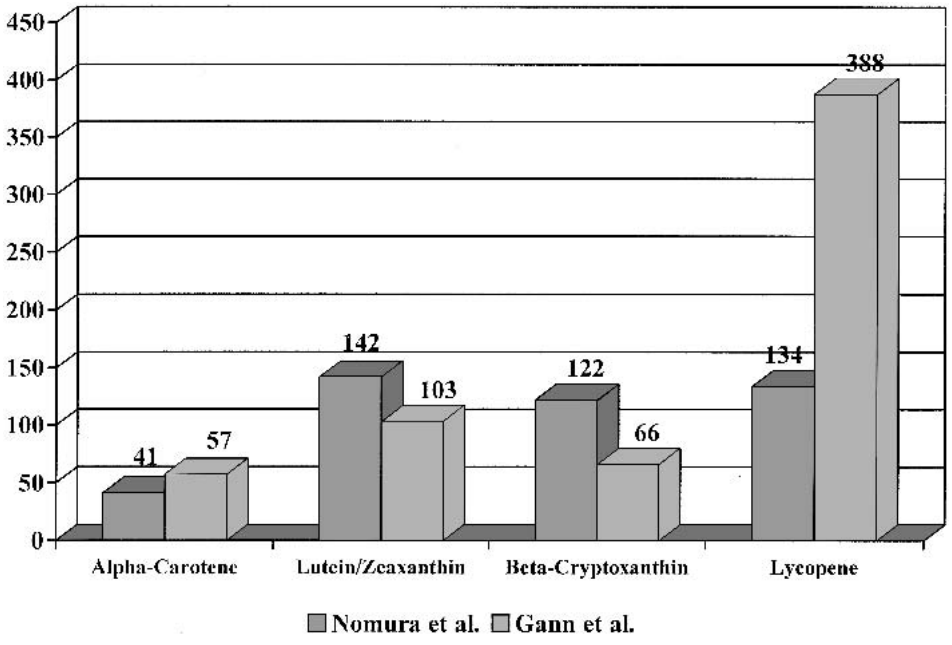

Figure 1. Comparison of mean circulating levels of carotenoids in the studies by Nomura *et al.* (34) and Gann *et al.* (33).

with the strongest and clearest association with prostate cancer (21). Clearly, current questionnaires that attempt to assess lycopene intake do not always capture true variation in the lycopene status in a given population, though for reasons that are not always apparent. Because of this unpredictability, unless there is a concurrent validation study, null studies should be interpreted with caution.

Future Directions

Overall, the dietary case-control and prospective studies, and the biomarker (lycopene) epidemiologic data suggest that intake of tomatoes and tomato products lower risk of prostate cancer, especially the more aggressive forms. This benefit may be related to lycopene, but other potential beneficial substances instead of or combined with lycopene cannot be excluded. Because the studies are not definitive, future work will be required. Other lines of evidence may provide additional information. A long-term large randomized trial with prostate cancer as the endpoint would certainly be informative, but may be impractical. Shorter-term trials using endpoints such as prostate cancer recurrence or intermediate endpoints may be more feasible.

Regarding any future epidemiologic studies, several features are critical to consider that would optimize the information from these studies. First, the complexity of the prostate cancer endpoint must be taken into account, especially in populations where PSA testing is widespread. Cancers in such populations are likely to be caught during earlier stages of progression, and will tend to be less lethal on average relative to those diagnosed in earlier studies. In the past, dietary as well other associations have often been primarily or limited to the subgroup of more lethal prostate cancers. Now, approximately 10% or less of men with prostate cancer have known metastatic disease at diagnosis (35), as opposed to almost one-half several decades ago; however, a substantial proportion of patients with apparently clinically localized disease will eventually develop metastatic disease (36, 37). Because the subgroup of newly diagnosed lesions that will progress is unknown, it is unclear for which subgroup factors such as lycopene may be most relevant. It is important for studies to examine more aggressive manifestations of prostate cancer because total prostate cancer itself is unlikely to be an adequate endpoint.

Second, the complexity in adequately assessing bioavailable lycopene must be taken into account. Plasma- or serum-based studies may be preferable, although the utility of a single measurement to assess long-term intake may differ among populations. Dietary-based studies would be enhanced by the inclusion of a blood sample, even in a subgroup, to assess how well lycopene is measured in that specific population, as well as to estimate the actual range of lycopene. Otherwise, it is difficult to interpret whether null results are caused by lack of a true association or by inadequate methodology.

Although not definitive, the available data suggest that increased consumption of tomato and tomato-based products may be prudent. In the Health Professionals Follow-Up Study, even 2–4 weekly servings of tomato sauce, an excellent source of bioavailable lycopene, reduced risk of total prostate cancer by one-third and aggressive prostate cancer by almost one-half. This recommendation is consistent with current guidelines to increase fruit and vegetable consumption to lower risk of cancer and other health conditions. There is unlikely to be adverse effects of tomato consumption, and perhaps other benefits may be evident (3). The specific use of lycopene-concentrated pills, however, needs to be evaluated in clinical trials before recommendations can be made. Also, the data available thus far have dealt only with tomato or lycopene intake prior to the diagnosis of cancer; the influence of tomatoes or lycopene on prognosis after the diagnosis of cancer requires evaluation.

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