REVIEW

Tomatoes, Tomato-Based Products, Lycopene, and Cancer: Review of the Epidemiologic Literature

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The epidemiologic literature in the English language regarding intake of tomatoes and tomato-based products and blood lycopene (a compound derived predominantly from tomatoes) level in relation to the risk of various cancers was reviewed. Among 72 studies identified, 57 reported inverse associations between tomato intake or blood lycopene level and the risk of cancer at a defined anatomic site; 35 of these inverse associations were statistically significant. No study indicated that higher tomato consumption or blood lycopene level statistically significantly increased the risk of cancer at any of the investigated sites. About half of the relative risks for comparisons of high with low intakes or levels for tomatoes or lycopene were approximately 0.6 or lower. The evidence for a benefit was strongest for cancers of the prostate, lung, and stomach. Data were also suggestive of a benefit for cancers of the pancreas, colon and rectum, esophagus, oral cavity, breast, and cervix. Because the data are from observational studies, a cause–effect relationship cannot be established definitively. However, the consistency of the results across numerous studies in diverse populations, for case–control and prospective studies, and for dietary-based and blood-based investigations argues against bias or confounding as the explanation for these findings. Lycopene may account for or contribute to these benefits, but this possibility is not yet proven and requires further study. Numerous other potentially beneficial compounds are present in tomatoes, and, conceivably, complex interactions among multiple components may contribute to the anticancer properties of tomatoes. The consistently lower risk of cancer for a variety of anatomic sites that is associated with higher consumption of tomatoes and tomato-based products adds further support for current dietary recommendations to increase fruit and vegetable consumption. [J Natl Cancer Inst 1999;91: 317–31]

Nutritional factors are widely believed to be critical in carcinogenesis *(1,2).* Overwhelming evidence from epidemiologic studies indicates that diets high in fruits and vegetables are associated with a lower risk of numerous cancers *(3–5).* Dietary recommendations to increase intake of citrus fruits, cruciferous vegetables, green and yellow vegetables, and fruits and vegetables high in vitamins A and C to lower cancer risk have been made by several organizations, including the National Research Council of the National Academy of Sciences *(1),* the National Cancer Institute *(6),* the American Cancer Society *(2,7),* and the World Cancer Research Fund and the American Institute for Cancer Research *(5).* However, uncertainty exists concerning which components account for this benefit.

Until recently, the health aspects of tomatoes had received relatively little attention. The antioxidant properties of lycopene, a carotenoid consumed largely from tomatoes, have raised interest in the tomato as a food with potential anticancer properties *(8).* Higher consumption of tomatoes is in fact compatible with current general recommendations aimed at increasing intake of fruits and vegetables. Nonetheless, whether unique benefits derive from tomatoes is important to establish because tomatoes are used in many processed items that are not necessarily identified with fruit or vegetable consumption. These items include tomato and spaghetti sauce, tomato soup, salsa, ketchup, and tomato paste. Moreover, many of these processed foods are better sources of bioavailable lycopene than are fresh tomatoes *(9–11).*

This review examines the epidemiologic evidence regarding consumption of tomato and related products with the risk of cancer at various body sites. The main purposes of this review are to assess the evidence for benefits by specific cancer site and to consider the strengths and limitations of the studies that help indicate whether observed associations are causal. Criteria considered include the strength of any associations, consistency of results by study design (case–control or cohort), method of exposure assessment (questionnaire or biomarker), the factors controlled for by matching or through data analysis, and the potential for residual or uncontrolled confounding. The potentially beneficial constituents of tomatoes and the implications for current dietary recommendations are then discussed.

Review of Epidemiologic Studies

All human studies reported in the English language of tomatoes or lycopene in relation to the risk of any cancer were considered. These studies were found in the MEDLINE® or CANCERLIT® databases and in several extensive reviews *(3–5),* or they were referenced in the identified studies. Because tomato intake or blood lycopene level was frequently one of numerous dietary factors examined, epidemiologic reports that had fruits, vegetables, or carotenoids as key words were scrutinized for results regarding tomato or lycopene. Two general types of study designs have been used to examine lycopene and tomato products in relation to risk of cancer. One study design has been based on a dietary questionnaire, used either to assess tomato products directly or to infer lycopene consumption; the other study design has been based on measuring levels of carotenoids in stored blood samples. Studies were summarized by type of

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design, years conducted, country, number of cases, main exposure assessment, relative risk (RR) with *P* values (two-sided) or confidence intervals (CIs), and covariates controlled for by matching or in analyses. The summarized RR is that for the cancer rate in the highest intake of tomatoes or level of lycopene divided by the rate in the lowest intake or plasma level. In case–control studies, the odds ratio was used to estimate the RR.

Total Cancer

Only one study has reported on tomato intake in relation to total cancer risk. In this prospective study by Colditz et al. *(12)*, based on 42 cancer deaths among 1271 elderly persons, individuals who were in the top half of tomato consumption had a lower risk of all cancers combined compared with those in the bottom half (RR = 0.5; 95% CI = 0.3–0.8). Other items, including green and yellow vegetables and strawberries, were also associated with a decreased risk of total cancer. Carrots and squash were unrelated to risk. There were too few cancers to allow examination of specific cancer sites.

Lung and Pleural Cancers

One of the cancer sites for which a benefit of fruits and vegetables has been most apparent is for cancers of the lung *(3)*, the leading cause of cancer death worldwide. Initial findings led investigators to focus on β-carotene and provided the impetus to examine supplemental β-carotene in relation to the risk of lung cancer in intervention trials. Unfortunately, the results from several trials either have been inconclusive *(13)* or have even indicated that smokers randomly assigned to receive β-carotene are at higher risk for lung cancer *(14,15)*.

Although the focus has been on β-carotene, the literature shows that several fruit and vegetable groups, including leafy green and yellow/orange vegetables, are associated with a lower risk of lung cancer *(3)*. Fourteen studies *(16–29)* have reported specifically on tomato or lycopene consumption in relation to lung cancer risk; of these, 10 *(17,18,20–24,26–28)* suggest either a statistically significant or a suggestive inverse association (Table 1). These studies, mostly case–control in design, generally adjusted for smoking history, the most important potential confounder for lung cancer. An additional study *(30)* indicated that higher prediagnostic dietary intake of tomatoes (recalled after diagnosis) among lung cancer case subjects was associated with better survival from lung cancer (Table 1). One study *(22)* found an inverse association between tomato intake and squamous cell and small-cell lung cancer but not with other histologic types. Statistically significant associations were observed in multiple U.S. populations, China, and Spain, and nonstatistically significant inverse associations were noted in the U.K., Norway, and Finland.

A case–control study in Hawaii by Le Marchand et al. *(17)* found tomato intake related to a substantially reduced risk of lung cancer; however, the same case–control dataset analyzed several years later for lycopene intake *(16)* indicated only a modest inverse association between lycopene intake and lung cancer risk that was not statistically significant. In this population, tomatoes accounted for only 29% of the reported lycopene intake. The conflicting results for tomato and lycopene intakes suggest that the benefit of tomatoes is related to compounds other than lycopene or that lycopene from non-tomato sources is not readily bioavailable.

Only one study that reported on mesothelioma (cancer of the pleura or peritoneum) was identified *(31)*. Overall, a 40% reduction in risk was noted for those consuming tomato or tomato juice 16 or more times a month versus nonconsumers. Only 1.7% of control subjects reported not consuming tomatoes or tomato juice as opposed to 9% of case subjects, suggesting nonconsumers of tomato products to be at relatively high risk for mesothelioma.

Stomach Cancer

Although becoming relatively uncommon in most economically developed countries, stomach or gastric cancer remains one of the major causes of cancer death in the world. Twelve case–control studies from a variety of populations, including the United States [New York *(32)*, Louisiana *(33)*, and Hawaiian Japanese *(34)*], Japan *(35)*, Israel *(36)*, Italy *(37–39)*, Spain *(40,41)*, Poland *(42)*, Belgium *(43)*, and Sweden *(44)* have reported data on tomato or lycopene intake and stomach cancer risk (Table 2). Inverse associations between tomato consumption and risk of gastric cancer were observed in all these diverse populations except for Spain *(40,41)* and Japan *(35)*. A suggestive, but not statistically significant, inverse association was observed in a study conducted in Belgium *(43)*, but this study population had a very low consumption of tomatoes. An ecologic study in Japan *(45)* that examined plasma levels of various nutrients in samples of populations in various regions found that regions high in plasma lycopene had the lowest gastric cancer rates and regions low in lycopene had the highest rates. While other fruits and vegetables have frequently been inversely associated with gastric cancer, inverse associations with tomatoes have been among the most consistent and strongest *(36–39,44)*. Although no prospective studies of tomato intake and gastric cancer were identified, the consistent inverse association observed in diverse populations strongly suggests a protective effect of tomato or lycopene consumption on gastric cancer.

Colorectal Cancer

Cancers of the colorectum are common in economically developed areas. Five studies *(37,46–50)* have reported on tomato intake in relation to colorectal cancer risk (Table 3). One study in the United States *(46)* reported statistically significant inverse associations between tomato consumption and colon cancer risk for men and women. A study in Belgium *(48)* found no overall association but did find a suggestion of an inverse association between consumption of tomato puree and colon cancer risk. The consumption of tomato products was low in this population, and the contrast was ever versus never consumption; the impact of higher intakes could not be assessed. Case–control studies in Italy *(37,50)* and China *(49)* reported about a 60% reduction in risk of both colon and rectal cancers associated with higher tomato consumption. In a rodent model of *N*-methylnitrosourea-induced colonic aberrant crypt foci, lycopene and lutein, but not β-carotene, in relatively small doses demonstrated efficacy against this premalignant lesion *(51)*.

Oral/Laryngeal/Pharyngeal Cancer

Only three case–control studies *(52–54)* have reported on tomato intake in relation to oral cancers (Table 3). One study in China *(52)* reported that high consumption of tomatoes was related to approximately half the risk of oral cancer. A similar finding was observed between tomato consumption and cancers

Table 1. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of the lung and pleura

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
Kvåle, 1983 *(22)*	Norway, United States	1964–1978	Cohort	168	Tomato intake, 6–13 vs. <1/mo	0.87, $P = .48$ (total) 0.54, $P = .07$ (squamous cell and small-cell)	Age, smoking status, region, urban/rural
Fraser, 1991 *(19)*	California, Seventh-day Adventists	1977–1982	Cohort	61	Tomato intake, ⩾7 vs. <3/wk	1.24 (0.51–2.99) $P = .79$	Age, sex, smoking status
Bond, 1987 *(23)*	Texas	1940–1980	Case–control	308	Tomato intake, 1/day vs. <1/mo	0.42 (0.14–1.33) P for trend = .05	Age, race, smoking status, educational level, vitamin supplement
Le Marchand, 1989 *(17)*, 1993 *(16)*	Hawaii	1983–1985	Case–control	230 ♂ 102 ♀	Tomatoes† Quintile 5 vs. 1 Lycopene intake Quintile 5 vs. 1	0.43, $P = .002$ ♂ 0.27, $P<.001$ ♀ 0.67, $P = .07$ ♂ 0.77, $P = .83$ ♀	Age, ethnicity, smoking status, pack-years, cholesterol intake
Harris, 1991 *(18)*	U.K.	1979–1981	Case–control	96 ♂	Tomato intake, >29.1 vs. <1 g/day	0.69, $P = .11$	Age, smoking status
Knekt, 1991 *(21)*	Finland	1966–1986	Cohort	117	Lycopene intake, μg, mean	684 ± 850 (mean ± standard deviation) case subjects 718 ± 895 (mean ± standard deviation) control subjects	Age
Candelora, 1992 *(27)*	Florida	1987–?	Case–control (nonsmokers)	124 ♀	Lycopene Quartile 4 vs. 1 Tomatoes Quartile 4 vs. 1	0.6 (0.3–1.2) $P = .13$ 0.7 (0.4–1.0)	Age, educational level, total calories, limited to nonsmokers
Forman, 1992 *(24)*	China	1985–1986	Case–control	183 ♂	Tomatoes Quartile 4 vs. 1	0.42 (0.19–0.96) $P = .04$	Age, educational level, body mass index, smoking status, income
Goodman, 1992 *(30)*	Hawaii	1979–1985	Prognosis (death)	463 ♂ 212 ♀	Tomatoes‡ Quartile 4 vs. 1 Prediagnostic diet	0.77, $P < .01$ ♂ 0.5, $P = .14$ ♀	Age at diagnosis, stage, histology, body mass index, smoking status
Steinmetz, 1993 *(25)*	Iowa	1986–1990	Cohort	138 ♀	Lycopene-rich food intake, ⩾5 vs. ⩽1/wk	1.21 (0.69–2.10) $P = .53$	Age, energy, smoking status
Mayne, 1994 *(20)*	New York State	1982–1985	Case–control	413	Tomato and tomato products Quartile 4 vs. 1	0.80, NS ♂ 0.76, NS ♀ 0.79, $P <.10$ ♂ and ♀	Age, cigarette smoking status, religion, educational level, body mass index, income
Muscat, 1996 *(31)*	New York	1985–1993	Case–control (mesothelioma)	94	Tomato/tomato juice intake, ⩾16 vs. 0/mo	0.6 (0.2–1.9)	Age, educational level, religion, occupation
Agudo, 1997 *(28)*	Spain	1989–1992	Case–control	103 ♀	Tomatoes High vs. low tertile	0.45 (0.22–0.91) $P = .026$	Age, smoking status, total pack-years
Comstock, 1997 *(29)*	Maryland	1989–1991	Cohort	258	Serum lycopene Quintile 5 vs. 1	1.01, P for trend = .97	Age, race, sex, date of blood donation, smoking status
Li, 1997 *(26)*	United States		Case–control (non-small cell)	93	Plasma lycopene Tertile 3 vs. 1	0.37, $P = .01$ African-Americans: 0.12, $P = .001$	Age, sex, race

*Relative risk and 95% confidence interval or P value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

†Tomatoes accounted for only 29% of total lycopene.

‡For squamous cell cancer only.

Table 2. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancer of the stomach

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
Haenszel, 1972 *(34)*	Hawaiian Japanese	1963–1969	Case–control	223	Tomato intake, ⩾11 vs. <4/mo	0.39, $P<.05$, all 0.31, $P<.08$, Issei 0.49, NS, Nisei	Age, sex
Modan, 1981 *(36)*	Israel	1967–1969	Case–control	406	Tomato intake, daily vs. never	0.55, P for trend <.0001	Age, sex, ethnic origin
Correa, 1985 *(33)*	Louisiana	1979–1983	Case–control	391	Tomatoes, "high vs. low" intake	0.82 (0.53–1.28), whites 0.56 (0.34–0.90), blacks	Age, sex, race, educational level, income, tobacco smoking status, alcohol intake
Tajima, 1985 *(35)*	Japan	1981–1983	Case–control	93	Tomatoes Tertile 3 vs. 1	1.24, NS	Age, sex
Franceschi, 1994 *(37)* La Vecchia, 1987 *(38)*	Italy (Milan)	1985–1991	Case–control	723	Tomatoes Quartile 4 vs. 1	0.43 (0.33–0.55)	Age, sex, study center, educational level, alcohol intake, tobacco smoking status, calories
Buiatti, 1989 *(39)*	Northern Italy	1985–1987	Case–control	1016	Tomatoes Tertile 3 vs. 1	0.70, P for trend <.001	Age, sex
Graham, 1990 *(32)*	New York	1975–1985	Case–control	293 (181 ♂)	Tomatoes	Decreasing risk Statistically significant for ♂ only	Age, sex, neighborhood
Boeing, 1991 *(42)*	Poland	1986–1990	Case–control	741	Tomatoes Tertile 3 vs. 1	0.77, P for trend = .03	Age, sex, occupation, educational level, residence
Gonzalez, 1991 *(41)*	Spain	1987–1989	Case–control	354	Tomatoes Quartile 4 vs. 1	0.9 (0.5–1.5)	Age, total calories, other food items
Ramón, 1993 *(40)*	Spain	1986–1989	Case–control	177	Tomatoes Tertile 3 vs. 1	1.03, NS	Age, sex
Tsugane, 1992 *(45)*	Japan	1985–1989	Ecologic		Plasma lycopene	Regions high in lycopene have lowest gastric cancer rates; low lycopene areas have highest cancer rates	Age
Tuyns, 1992 *(43)*	Belgium	1979–1982	Case–control	449	Cooked tomato intake, >0 vs. 0 Raw tomato intake, >10 vs. 0 g/wk	0.12, $P = .50$ 0.74, $P = .08$	Age, sex, province, other vegetables
Hansson, 1993 *(44)*	Sweden	1989–1992	Case–control	456	Adolescence, >3 vs. 0/mo 20 y prior >15 vs. <2/mo	0.36 (0.23–0.58) $P<.0001$ 0.72 (0.47–1.11) $P = .015$	Age, sex, socioeconomic status

*Relative risk and 95% confidence interval or P value (two-sided) for exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

of the oral cavity and pharynx in Italy *(54)*. A study of tomato consumption and laryngeal cancer in China *(53)* did not find an association.

Esophageal Cancer

Esophageal cancers have received little study regarding tomatoes and lycopene (Table 3). One study in Iran *(55)*, which has extremely high rates of esophageal cancer particularly in men, found a 39% statistically significant reduction in risk for men who consumed tomatoes frequently, but no relationship was apparent for women. The only other diet-based study reported for this cancer, conducted in the United States *(56)*, reported a 30% nonstatistically significant reduction in esophageal cancer risk associated with high tomato consumption in men. A serum bank-based study by Nomura et al. *(57)* reported that case patients with oral, laryngeal, or esophageal cancers had a 5% lower mean prediagnostic serum lycopene level than control subjects that was not statistically significant; however, on the basis of only 28 case patients with esophageal cancer, case patients had a 16.4% lower lycopene level ($P = .08$).

Pancreatic Cancer

Four studies *(58–61)* have examined tomato or lycopene status in relation to risk of pancreatic cancer; all of these studies support an inverse association (Table 3). Two studies *(58,61)* reported an inverse association but did not provide estimates of

Table 3. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of the digestive tract (excluding stomach)*

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk† (95% confidence interval)	Adjusted factors
				Colorectal cancer			
Tuyns, 1988 *(48)*	Belgium	1978–1982	Case–control (colon, rectal)	453 C 365 R	Tomato intake, >0 vs. 0 g/wk Tomato puree intake, >0 vs. 0 g/wk	1.15, $P = .31$ C 1.03, $P = .84$ R 0.78, $P = .12$ C 0.93, $P = .93$ R	Age, sex, province
Freudenheim, 1990 *(46)*	New York State	1978–1986	Case–control (rectal)	277 ♂ 145 ♀	Tomatoes	SS decreased risk SS decreased risk	Age
Hu, 1991 *(49)*	China	1985–1988	Case–control (colon, rectal)	111 C 225 R	1966 diet (>15 kg/y) 1985 diet (>15 kg/y) ♂ rectal 1966 >20 kg/y	0.40 (0.17–0.94) C♂ 0.26 (0.12–0.55) C♀ 0.40 (0.17–0.94) R♂ NS R♀	Univariate
Centonze, 1994 *(47)*	Southern Italy	1987–1989	Case–control (colorectal)	132	Pizza, high vs. low intake	0.89 (0.51–1.53) $P = .66$	Age, sex, educational level, smoking status, modification of diet in past
Franceschi, 1994 *(37)* Franceschi, 1997 *(50)*	Northern Italy	1985–1991	Case–control (colon, rectal)	955 C 629 R	Tomatoes Quartile 4 vs. 1	0.39 (0.31–0.49) C 0.42 (0.32–0.55) R	Age, sex, study center, educational level, calories, alcohol intake, smoking status
				Oral cancers			
Franceschi, 1991 *(54)*	Northern Italy	1985–?	Case–control (oral and pharynx)	266 ♂ 36 ♀	Fresh tomatoes Tertile 3 vs. 1	0.5, $P<.01$	Age, sex, occupation, smoking status, alcohol intake, other significant foods
Zheng, 1992 *(53)*	China	1988–1990	Case–control (larynx)	177 ♂ 24 ♀	Tomatoes Tertile 3 vs. 1	1.2, $P = .45$ ♂ 1.1 (0.4–3.1) ♀	Age, educational level, smoking status
Zheng, 1993 *(52)*	China	1989	Case–control (oral)	404	Tomato intake, ⩾1/day vs. ⩽3/wk	0.49 (0.26–0.94)	Age, tobacco smoking status, alcohol intake, dentition, body mass index, energy, educational level, sex
				Esophageal and laryngeal cancers			
Cook-Mozaffari, 1979 *(55)*	Iran	1975–1976	Case–control (esophagus)	217 ♂ 127 ♀	Raw tomato intake, ⩾1/wk vs. <1/mo	0.61 (0.43–0.86) ♂ 1.08 (0.69–1.67) ♀	Age, region
Brown, 1988 *(56)*	South Carolina	1982–1984	Case–control (esophagus)	207 ♂	Tomatoes, high vs. low intake	0.70 (0.4–1.4)	Age, cigarette smoking status, alcohol intake
Nomura, 1997 *(57)*	Hawaii	1971–1991	Cohort (esophagus and larynx)	69	Serum lycopene (mean)	Case subjects 19.1 ± 1.4 (mean ± standard error) Control subjects 21.1 ± 1.0 (mean ± standard error) $P = .27$	Age, smoking history (detailed), alcohol intake
				Pancreatic cancer			
Mills, 1988 *(58)*	Seventh-day Adventists	1976–1983	Cohort (fatal)	50	Tomatoes	Inverse association (na)	Age
Burney, 1989 *(59)*	Maryland	1975–1986	Cohort	22	Serum lycopene High vs. lowest 2 tertiles	0.16 (0.04–0.57) P for trend <.02	Age, sex, race, hours since last meal, smoking status, educational level
Baghurst, 1991 *(61)*	Australia	1984–1987	Case–control	104	Tomatoes	Inverse trend, $P<.05$, ♂ only	Age
Bueno de Mesquita, 1991 *(60)*	The Netherlands	1984–1988	Case–control	164	Tomatoes Quintile 5 vs. 1	0.23, $P<.05$	Age, sex, smoking status, energy

*C = colon; R = rectum.

†Relative risk and 95% confidence interval or P value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. SS = statistically significant; NS = not significant; na = P value not available.

RR. The two that reported the magnitude of the RR found about a fourfold to fivefold risk elevation among low consumers of tomatoes *(60)* or among those with low levels of serum lycopene collected prospectively in a case–control study nested within a cohort *(59)*. Although the serum-based study *(59)* involved only 22 case patients, the results were statistically significant ($P<.02$), and no association was seen with total carotenoids or β-carotene. It is unlikely that low lycopene levels were the result of the cancer because the relationship was apparent in cancers diagnosed 9–12 years after collection of the blood and pancreatic cancers are rapidly progressive and thus have a short latent period. Also suggestive of a specific effect of lycopene among carotenoids, the dietary-based study by Bueno de Mesquita et al. *(60)* did not find a benefit of carrots, a major source of β-carotene and α-carotene.

Prostate Cancer

Four cohort studies *(62–65)* report data on the relationship between tomato or lycopene consumption and prostate cancer risk (Table 4). In a cohort of 14 000 Seventh-day Adventist men *(62)*, only tomato intake and intake of beans, lentils, and peas were statistically significantly related to lower prostate cancer risk in a multivariate analysis. β-Carotene-rich foods were unrelated to risk. In a larger, more comprehensive dietary study *(64)*, intake of the carotenoids β-carotene, α-carotene, lutein, and β-cryptoxanthin was not associated with risk of prostate cancer, but high lycopene intake was related to a statistically significant 21% reduction in risk. High intake of tomatoes and tomato products, which accounted for 82% of lycopene, reduced risk of total prostate cancer by 35% and aggressive prostate cancer by 53%. Tomato sauce had the strongest inverse association with prostate cancer risk (RR = 0.66; 95% CI = 0.49–0.90; P for trend = .001), and weaker inverse associations were observed with tomatoes and pizza, but none with tomato juice. Preliminary results from two other cohort studies *(63,65)* also support this finding.

One case–control study conducted in Minnesota *(66)* found an inverse association between tomato intake and risk of prostate cancer that was not statistically significant. In another case–control study conducted in a multiethnic population in Hawaii *(67)*, no association was found 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. A case–control study conducted in the U.K. *(68)* found no association between raw or cooked tomatoes and risk of prostate cancer. Of note, the strongest dietary association found in that study was for baked beans (RR = 0.52; 95% CI = 0.31–0.88); the authors suggest that tinned baked beans may provide highly bioavailable lycopene from the tomato sauce.

Three studies *(69–71)* have examined serum carotenoids using prediagnostic samples in relation to prostate cancer risk. The first study *(69)*, which was based on serum obtained in 1974 from 25 802 persons in Washington County, MD, found a 6.2% lower median lycopene level in prostate cancer case subjects diagnosed during 13 years compared with age- and race-matched control subjects. The estimated RR was 0.50 (95% CI = 0.20–1.29) between high and low quartiles of lycopene. No other carotenoid was associated with prostate cancer risk. Preliminary results from the Physicians' Health Study *(70)*, which was based on 581 case subjects, found a statistically significant RR of 0.56 (95% CI = 0.34–0.91) when comparing high quintile with low quintile of plasma lycopene.

A serum-based study conducted during the period from 1971 through 1993 in a Japanese-American population in Hawaii *(71)* did not detect any association between serum lycopene levels and risk of prostate cancer. However, several characteristics of the study may have contributed to the lack of an association, including use of a single assessment of serum lycopene to characterize follow-up for up to a 22-year period (only 14 cases occurred within the first 5 years of follow-up), inclusion of "low virulence" disease (28% were diagnosed incidentally during surgery for benign prostatic hyperplasia), and very low serum lycopene levels [the median serum concentration among control subjects was only 134 ng/mL, compared with 320 ng/mL in the study by Hsing et al. *(69)* and 424 ng/mL in the sample of 121 health professionals *(64)*]. Ethnic differences in prostate cancer etiology may also be important, inasmuch as men of Asian descent may have an inherently low susceptibility to prostate cancer.

Bladder Cancer

Four reports of tomato or lycopene consumption *(72–74)* or serum lycopene *(75)* and risk of bladder cancer were identified (Table 4). None of these studies found statistically significant associations with risk of bladder cancer, although tendencies for inverse associations were noted. Results from the sole serum-based study *(75)* were suggestive of an inverse trend (RR = 0.5; P for trend = .06). However, that study was based on only 35 case subjects. Unpublished data from a prospective cohort study of male health professionals do not indicate any association between consumption of tomato-based products or lycopene and bladder cancer (251 cases). A strong inverse association between tomato-based product intake and risk of prostate cancer was found in the same cohort *(64)*. In a rat model of urinary superficial bladder cancer induced by nitrosamines, lycopene demonstrated modest anticancer properties *(76)*.

Breast Cancer

For breast cancer, a common cause of cancer in Western countries, an overall benefit of fruits and vegetables is suggested but is not as clearly apparent as for several other cancer sites *(3,4)*. Considering the importance of this disease, relatively few studies have examined its relationship to tomato or lycopene intake (Table 5). Dietary-based studies *(77–80)* do not support an association between tomato intake and risk of breast cancer, although relatively few studies have reported on this. However, of four studies *(81–84)* based on biomarkers (blood level or breast adipose level) of lycopene, three *(81,82,84)* support a benefit, two of which were statistically significant *(81,82)*. The small study *(81)* based on adipose levels of carotenoids in breast tissue from case and control subjects did find statistically significantly lower concentrations of lycopene among case subjects, although an impact of the cancer on tissue lycopene levels cannot be excluded. Of note, breast adipose tissue lycopene was weakly correlated with lycopene intake estimated by a food-frequency questionnaire in that study ($r = .17$). It is possible that a low correlation between reported intake and tissue level, whether due to measurement or biologic reasons, could account for the generally null results from dietary studies for breast cancer. Lycopene also has been shown to have antiproliferative effects against breast cancer cells in culture *(85)*, and tomato oleoresin-treated rats developed fewer 7,12-dimethyl-

Table 4. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancer of the genitourinary tract

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
				Prostate cancer			
Schuman, 1982 *(66)*	Minnesota	1976–1979	Case–control	223	Tomatoes, high vs. low intake	0.70, NS	Age
Mills, 1989 *(62)*	California Seventh-day Adventists	1974–1982	Cohort	180	Tomato intake, ⩾5 vs. <1/wk	0.60 (0.37–0.97) $P = .02$	Age, educational level, consumption of meat, poultry, fish, beans, legumes, peas, citrus fruit, nuts, or fruits
Hsing, 1990 *(69)*	Maryland	1974–1985	Cohort	103	Serum lycopene Quartile 4 vs. 1	0.50 (0.20–1.29) $P = .26$	Age, smoking status, race, educational level, hours since last meal
Le Marchand, 1991 *(67)*	Hawaii	1970–1983	Case–control	452	Lycopene Quartile 4 vs. 1	0.9 $P = .35$, <70 y 1.1, $P = .57$, ⩾70 y	Age, ethnicity
Giovannucci, 1995 *(64)*	United States	1986–1992	Cohort	773	Dietary tomato-based products, >10 vs. <1.5 servings/wk	0.65 (0.44–0.95) $P = .01$	Age, total energy, ancestry, vasectomy, animal fat, retinol
					Tomato sauce intake, 2–4 vs. 0/wk	0.66 (0.49–0.90) $P = .001$	
Baldwin, 1997 (abstract) *(65)*	California	1995	Cohort retrospective		"Consistently high tomato consumption"	0.59, $P = .03$	—
Key, 1997 *(68)*	U.K.	1989–1992	Case–control	328	Dietary lycopene intake, ⩾718 μg vs. <402 μg	0.99 (0.68–1.45) $P = .88$	Age, social class
					Raw tomato intake, ⩾5/wk vs. ⩽3/mo	1.06 (0.55–1.62) $P = .88$	
					Cooked tomato intake, ⩾2/wk vs. <1/mo	0.92 (0.57–1.42) $P = .64$	
Nomura, 1997 *(71)*	Hawaii	1971–1993	Cohort	142	Serum lycopene Quartile 4 vs. 1	1.1 (0.5–2.2) $P = 0.86$	Age
Cerhan, 1998 (abstract) *(63)*	United States	1987–1990	Cohort	101	Dietary tomatoes Quintile 5 vs. 1	0.50 (0.3–0.9) $P = .03$	Age, total energy, other dietary and nondietary factors
Gann, 1998 (abstract) *(70)*	United States	1982–1995	Cohort	581	Plasma lycopene Quintile 5 vs. 1	0.56 (0.34–0.91) $P = .05$	Age, smoking status, body mass index, alcohol consumption, exercise, multivitamin use, plasma cholesterol level
				Bladder cancer			
Helzlsouer, 1989 *(75)*	Maryland	1974–1986	Cohort	35	Serum lycopene Tertile 3 vs. 1	0.5, P for trend = .06	Age, sex, race, interval since last meal
Nomura, 1991 *(74)*	Hawaii	1977–1986	Case–control	195 ♂ 66 ♀	Lycopene Quintile 5 vs. 1	0.7, P for trend = .27 ♂ 0.9, P for trend = .41 ♀	Age, cigarette pack-years
Riboli, 1991 *(73)*	Spain	1985–1986	Case–control	432 ♂	Tomatoes	No association	Age
Bruemmer, 1996 *(72)*	Washington State	1987–1990	Case–control	262	Tomato intake, >0.29 vs. ⩽0.07/day	0.71 (0.39–1.29) P for trend = .13	Age, sex, county, smoking status, calories

*Relative risk and 95% confidence interval or P value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

benz[*a*]anthracene-induced mammary tumors, whereas β-carotene had no effect *(86)*.

Cervical Cancer and Precursors

Two studies have reported on tomato consumption and risk of cervical cancer *(87,88)*, and three have examined serum lycopene in relation to cervical cancer *(89,90)* or precursor lesions *(91)* (Table 5). Monthly tomato consumption was higher in control subjects than in case subjects in one case–control study *(87)*, although this finding did not attain statistical significance. A study in The Netherlands *(88)* found women who consumed tomatoes three or more times a week to have a 40% reduction in

Table 5. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of female reproductive organs

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
				Breast cancer			
Ewertz, 1990 *(79)*	Denmark	1983–1984	Case–control	1486	Tomatoes Quartile 4 vs. 1	1.04 (0.79–1.31)	Age, residence
Potischman, 1990 *(84)*	New York State	1985–1986	Case–control	83	Plasma lycopene Quartile 4 vs. 1	0.62 (0.19–2.0) $P = .43$	Age, age at first birth, family history of cancer, age at menarche, body mass index, age at menopause, income, marital status, plasma cholesterol level, triglyceride level
London, 1992 *(83)*	Massachusetts	1986–1988	Case–control	377	Serum lycopene Quintile 5 vs. 1	1.0 (0.7–1.7)	Age, alcohol consumption, age at first birth, parity, family history of cancer, age at menopause, age at menarche, body weight, benign breast disease
Levi, 1993 *(78)*	Switzerland	1990–1992	Case–control	107	Tomatoes Tertile 3 vs. 1	0.9, NS	Age
Freudenheim, 1996 *(80)*	New York State	1986–1991	Case–control	297	Lycopene intake, ⩾7123 μg/day vs. ⩽3775 μg/day	0.87 (0.55–1.39) $P = .24$	Age, educational level, age at first birth, age at menarche, family history of cancer, benign breast disease, body mass index, energy
Järvinen, 1997 *(77)*	Finland	1967–1992	Cohort	88	Lycopene Tertile 3 vs. 1	~1.0	Age, body mass index, parity, region, smoking status, occupation
Zhang, 1997 *(81)*	Massachusetts	1989–1992	Case–control (breast adipose)	46	Breast adipose lycopene levels, ⩾ vs. < median	0.32 (0.11–0.94)	Age, smoking status, menopausal status
Dorgan, 1998 *(82)*	Missouri	1977–1987	Cohort	105	Serum lycopene levels, >0.51 μmol/L vs. ⩽0.22 μmol/L	0.5 (0.2–1.2) $P = .02$	Age, benign breast disease, serum cholesterol level, cigarette smoking status, body mass index
				Cervical cancer			
Marshall, 1983 *(87)*	New York State	1957–1965	Case–control	513	Tomato intake, mean monthly servings	8.02, case subject 8.49, control subject $P = .2$	Age
de Vet, 1991 *(88)*	The Netherlands	1984–1987	Case–control (cervical dysplasia)	257	Tomato intake, ⩾3 vs. 0/wk	0.58 (0.33–1.02) $P = .01$	Age, demographics, marital status, educational level, smoking status, children, contraception, age at first intercourse, frequency of intercourse, sexual partners, frequency of pap smear, other food group consumption
Potischman, 1991 *(89)*	Latin America	1986–1987	Case–control	387	Serum lycopene level, >21.4 μg/dL vs. <6.4 μg/dL	1.14 (0.8–2.1) $P = .69$	Age, study site, age at first intercourse, No. of sex partners, No. of pregnancies, Pap smear, papillomavirus 16/18, No. of household facilities, cholesterol level, level of triglycerides

Table 5 (continued). Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of female reproductive organs

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
VanEenwyk, 1991 *(91)*	Illinois	1987–1989	Case–control (cervical intraepithelial neoplasm I, II, or III)	102	Serum lycopene level, >41.3 μg/dL vs. <21.3 μg/dL	0.26 (0.08–0.9) $P = .004$	Age, smoking status, income, vitamin C, Pap smear frequency, spermicidal contraception, genital warts, body mass index
					Diet lycopene Quartile 4 vs. 1	0.19 (0.04–0.77) $P = .02$	
Batieha, 1993 *(90)*	Maryland	1975–1990	Case–control	50† 18 (invasive) 32 (carcinoma *in situ*)	Serum lycopene level, >41.8 μg/dL vs. <24.9 μg/dL	0.40 (0.15–1.04) $P = .08$	Age, race, time since last meal
				Ovarian cancer			
Helzlsouer, 1996 *(92)*	Maryland	1974–1989	Cohort	35	Serum lycopene level, >35.2 μg/dL vs. <21.9 μg/dL	1.36 (0.4–4.3) $P = .59$	Age, menstrual status, hours since last meal prior to collection

*Relative risk and 95% confidence interval or *P* value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

†The relative risk is only for all 50 cases; the 50 cases comprise 18 invasive carcinomas and 32 carcinomas *in situ;* results are not presented for the 18 and 32 cases individually.

risk of cervical dysplasia relative to nonconsumers. One study *(89)* found no association between serum lycopene and risk of cervical cancer, but another study *(90)* found a borderline statistically significant inverse association between serum lycopene and risk of invasive (n = 18) or preinvasive (n = 32) cervical cancer. A study of cervical cancer precursor lesions (cervical intraepithelial neoplasm [CIN] I, II, III) *(91)* found a fourfold higher risk in women with low serum lycopene levels and a fivefold excess risk among those with low dietary lycopene levels. Thus, three of three studies of preinvasive lesions reported an inverse association with tomato intake *(88)* or serum lycopene *(90,91).* In one study *(90),* levels of serum carotenoids were also related to lower risk, whereas the study by VanEenwyk et al. *(91)* found benefits only for lycopene.

Ovarian Cancer

Only one study that reported data regarding tomato or lycopene and ovarian cancer was found. This was a prospective serum-based study of 35 case subjects (Table 5) *(92).* This small study indicated no association, although the mean level of serum lycopene in the case subjects was 7.4% lower than in the control subjects. More study of this cancer is clearly required before firmer conclusions can be reached.

Summary of Epidemiologic Evidence

Consistency of Results

Including studies that have reported results but did not specify RRs, 72 studies have reported on intake of tomatoes, tomato-based products, and lycopene or blood or tissue level of lycopene and risk of a cancer site. These were based on 66 reports, some of which separately analyzed various cancer sites (e.g., colon and rectum). Of these 72 studies, 57 found inverse associations between tomato or lycopene consumption or blood lycopene level and risk of cancer; 35 of these inverse associations were statistically significant. The remaining 15 studies were inconclusive or indicated a slight direct association, with RRs mostly within the range between 1.0 and 1.2. No statistically significant direct association between tomato or lycopene consumption and risk for any cancer site was noted.

Table 6 shows the RRs from 61 studies that provide data; there are 74 RRs because some studies present results stratified by sex, racial or ethnic group, colon and rectum cancers separately, and results both for blood lycopene level and for dietary tomato or lycopene intakes. Almost half the studies found RRs around 0.6 or less, about two thirds with RRs less than 0.8. The results did not vary appreciably whether they were based

Table 6. Summary of the relative risks for high versus low intakes (levels) of tomatoes (lycopene) across the study characteristics

Study type	Total No. (%)	No. (%) by relative risk ⩽0.6	0.61–0.8	0.81–1.0	>1.0
Cohort	16 (100)	10 (63)	0 (0)	1 (6)	5 (31)
Case–control	58 (100)	26 (45)	13 (22)	10 (17)	9 (16)
Diet based	59 (100)	27 (46)	12 (20)	11 (19)	9 (15)
Biomarker* based	15 (100)	9 (60)	1 (7)	0 (0)	5 (33)
Both sexes	33 (100)	18 (55)	5 (15)	6 (18)	4 (12)
Male	20 (100)	10 (50)	6 (30)	2 (10)	2 (10)
Female	21 (100)	8 (38)	2 (10)	3 (14)	8 (38)
Total†	74 (100)	36 (49)	13 (18)	11 (15)	14 (19)

*14 blood-based and one study based on lycopene level in breast adipose tissue.

†From 61 studies that provided data *(17–20,22–29,31,33–37,39–44,47–49,52–56,59,60,62–72,74,75,77–84,86,88–92);* there are 74 relative risks because some studies present results stratified by sex, racial or ethnic group, colon and rectum cancers separately, and results both for blood lycopene level and for dietary tomato or lycopene intakes.

on prospective or retrospective data or whether they were based on dietary intakes or blood lycopene levels. The RRs (two-sided *P* values) for biomarker-based studies are 0.16 ($P<.02$), 0.26 ($P = .004$), 0.32 ($P<.05$), 0.37 ($P = .01$), 0.4 ($P = .08$), 0.5 ($P = .02$), 0.5 ($P = .06$), 0.50 ($P = .26$), 0.56 ($P = .05$), 0.62 (not significant), 1.01 ($P = .97$), 1.0 (not significant), 1.1 ($P = .86$), 1.14 ($P = .69$), and 1.36 ($P = .59$). Of these 15 studies, 10 had RRs less than or equal to 0.62, and eight were statistically significant or of borderline statistical significance ($P \leqslant .08$), and in five of the studies *(59,69,70, 75,91)*, an inverse relationship was limited to lycopene among carotenoids.

Comparisons by sex tended to show more studies with inverse associations for males, but most studies also supported a benefit for women (Table 6). Cancers, such as those of the lung or stomach, for which both sexes are at risk, do not indicate strong differences in findings by sex. Evidence for a benefit was strong for prostate cancer. For several female-associated cancers, particularly cancers of the ovary and endometrium, data are very sparse.

RR estimates for the various cancers are shown in Fig. 1. The tendency for an inverse association between consumption of tomatoes or tomato products or lycopene levels is observed for a variety of cancer sites. The data are most compelling for cancers of the prostate gland, lung, and stomach. Data are also suggestive for several other cancers, including pancreatic, colorectal, esophageal, oral, breast, and cervical cancers. Data regarding the relationship between tomato consumption or lycopene level and cancer risk for other cancer sites are too limited at present to support firm conclusions.

In summary, the epidemiologic data indicate that high consumers of tomatoes and tomato products are at substantially decreased risk of numerous cancers, although probably not all cancers. The results are consistent for a variety of cancers across numerous diverse populations and with the use of different types of study designs. These include ecologic, case–control dietary studies, prospective dietary studies, and blood specimen-based investigations. Because the evidence available is based on observational studies, and thus causality cannot be directly inferred, the possibility for biases and confounding is considered next.

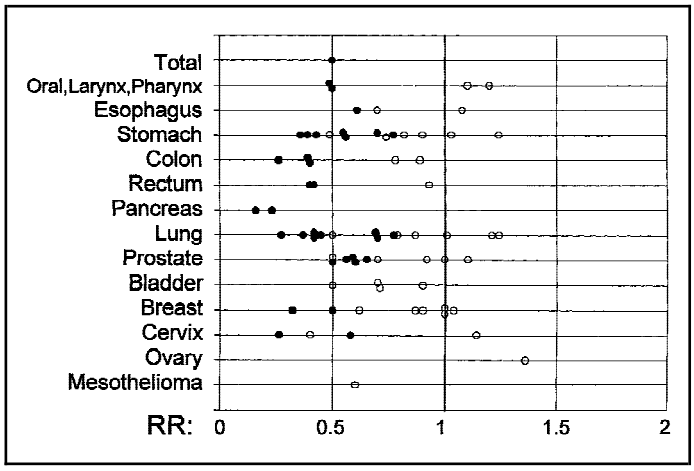

Fig. 1. Summary relative risks (RR) for high versus low consumption of tomatoes or level of lycopene from epidemiologic studies. ● = statistically significant; ○ = not statistically significant.

Potential for Bias and Confounding as Explaining the Results

Biases occur when, through faulty data-collection techniques, the associations in the study population are distorted. For example, in some case–control studies, for which the disease status is known at the time of interview, case subjects may recall past diet differently from control subjects. Biases possibly may have occurred in specific settings, but that a single, strong methodologic bias accounts for all these findings is not plausible. Recall biases, for instance, cannot account for associations observed in prospective studies, particularly those based on blood levels of lycopene rather than on dietary recall.

Publication bias (e.g., results reported in the literature only from studies that found a relationship) is unlikely to be of major importance for our overall findings because, if no underlying association existed, one would expect as many direct associations as inverse associations to be reported. Here, 35 statistically significant inverse associations were identified, but none with direct associations were found. However, for specific cancer sites for which only a small number of reports have been published, selective publication may be a potential factor.

Although systematic errors or bias in reporting tomato or lycopene intake cannot account for all the findings, it is possible that the association between high tomato consumption and lower risk for numerous cancers is not causal but rather is secondary to some confounding factor(s) associated with tomato intake. This possibility cannot be ruled out entirely, but it is unlikely for several reasons. For confounding to occur, the confounding factor has to be simultaneously an important risk or protective factor for that cancer and correlated substantially with tomato intake. As shown in the tables, known or suspected risk factors were controlled for in many of the studies. In general, confounding from the considered factors did not account for the observed relationships.

It is possible that some unidentified confounding factor accounted for these associations. However, given the variety of cancers studied, the different etiologies for cancers, and the diversity of populations studies, uncontrolled confounding is unlikely to account for most of the inverse associations with tomatoes or lycopene. The pattern of potentially confounding factors for tomato products will likely vary among cancers, which have different risk factors. Moreover, dietary patterns differ among countries, and at least one statistically significant inverse association for tomato products was observed in 10 countries (United States, Italy, Holland, Spain, Sweden, Poland, Australia, Iran, China, and Japan). The pattern of covariates will also likely vary by type of tomato product. For example, in the Health Professionals Follow-up Study *(64)*, fresh tomatoes tended to be associated with "healthy" lifestyle practices, tomato sauce displayed no discernible pattern, and pizza was associated slightly with "unhealthy" practices, yet all three items were inversely associated with risk of prostate cancer.

The inverse association between plasma lycopene level and cancers of the prostate, lung, cervix, breast, and pancreas is particularly interesting because plasma and tissue lycopene levels are poorly correlated with overall vegetable and fruit intake because of the diverse nature of tomato products [$r = .11$ *(93)*; $r = .11$ in women and .16 in men *(94)*]. Unlike lycopene levels, most other carotenoid levels correlate reasonably well with vegetable and fruit intake *(93,94)*. Furthermore, in a study of a

general U.S. population, lower serum concentrations of β-carotene, α-carotene, lutein, and β-cryptoxanthin were generally associated with male sex, higher alcohol intake, increased smoking, and higher body mass index; dietary and serum lycopene levels were not associated with these factors *(95)*. Thus, it is unlikely that the inverse association between plasma lycopene level and risk of various cancers is a result of lycopene's being a nonspecific marker of fruit and vegetable intake or related "healthy" behaviors.

Dose–Response Relationship

Although most studies indicate an anticancer benefit of tomato consumption, it is difficult to draw firm conclusions regarding the dose–response relationship. For the most part, RRs appeared to decrease proportionally to increasing intake of tomatoes or related products. Within the observable range, there was no firm evidence of an intake level where the trend toward decreasing risk begins to reverse, although few data are available regarding intakes of tomatoes or tomato-based products exceeding one serving per day. Caution is advisable regarding pharmacologic doses of lycopene because all of the epidemiologic data are based on typical dietary intakes. Moreover, one animal study of lung cancer *(96)* suggests a benefit of lycopene intake at lower levels but possibly an adverse effect of lycopene intake at very high levels. Benefits may also vary by the specific type of tomato products because processing and cooking may influence the level or bioavailability of the bioactive compounds (e.g., lycopene).

Potentially Beneficial Aspects of Tomatoes and Tomato-Based Products

Tomato and tomato-based products are important sources of many established nutrients and are predominant sources of some phytochemicals that may have health benefits. Tomatoes are relatively rich sources of folate, vitamin C, vitamin A, and potassium. Because other good sources of these nutrients are available, the relative importance of tomatoes as contributors of these nutrients varies across populations. In the United States, consumption of tomatoes and tomato products ranks number two to potatoes among vegetables *(97)*. Because they are highly consumed, tomatoes and related products rank as the number three contributor of vitamin C and the number four contributor of provitamin A and are the ninth highest contributor of potassium to the U.S. diet. In Italy, tomatoes have been estimated as the second most important source of vitamin C after oranges *(98)*. In contrast, tomato consumption in some populations appears to be too low for them to be a good source of these nutrients [e.g., the study by Tuyns et al. *(43)* in Belgium]. Anticancer properties for several of these nutrients have been hypothesized.

In addition to being a substantial source of some traditional nutrients, tomatoes are rich in several phytochemicals believed to have anticancer properties. Among the most prominent phytochemicals in tomatoes are the carotenoids, important pigments found in plants, and photosynthetic bacteria, fungi, and algae. These organisms synthesize phytoene, a 40-carbon molecule with 9 double bonds (in the *trans* configuration), which serves as a precursor for more than 600 carotenoids. A series of desaturation steps leads sequentially to phytofluene, ζ-carotene, neurosporene, and lycopene, a symmetrical, acyclic 40-carbon molecule with 13 double bonds (11 conjugated). Enzymatic cyclization of the end groups of lycopene results in γ-carotene (one β-ionone ring) and β-carotene (two β-ionone rings). The β-ionone rings are critical for vitamin A activity; other ring structures formed are devoid of vitamin A activity. Thus, cleavage of γ-carotene forms one vitamin A molecule, while cleavage of β-carotene leads to two vitamin A molecules. Oxygenation of the β-ionone rings leads to the more polar oxycarotenoids or xanthophils, such as β-cryptoxanthin (one oxygenated ring, half the provitamin A activity of β-carotene) and lutein (two oxygenated rings and hence no provitamin A activity).

Plants vary substantially in their overall production of carotenoids and in the activities of various enzymes involved in desaturation, cyclization, and oxygenation to produce a wide range of carotenoids. For example, the red color of tomatoes results from lycopene, suggesting that red tomatoes have insufficient cyclase activity to convert lycopene to γ-carotene and β-carotene efficiently. Variation in different strains of tomatoes exists, as evidenced by yellow tomatoes, which are relatively low in lycopene. Among foods typically consumed by humans, tomatoes are a particularly rich source of several carotenoids. Of 14 carotenoids found in human serum, tomato and tomato-based products contribute to nine and are the predominant source of about half of the carotenoids *(99)*. Tomatoes are low in β-carotene (most of the provitamin A activity from tomatoes is from γ-carotene) and low in the polar xanthophils, but they are by far the major source of the remaining nonpolar carotenoids.

Overall, tomatoes are an important source of several nutrients and a predominant source of several carotenoids, particularly lycopene. Very few items other than tomato products contribute to dietary lycopene; these include watermelon, pink grapefruit, and apricots. Tomatoes are also a source of other potentially beneficial phytochemicals, including phenylpropanoids (phenolic acids), phytosterols, and flavonoids *(97)*. However, the biologic relevance of these latter compounds, plus the relative importance of tomatoes as a dietary source of these, is unknown.

Biologic Plausibility of an Anticancer Effect of Lycopene

Lycopene has received the most attention, but whether apparent anticancer properties of tomatoes result from lycopene remains unproven. Nonetheless, lycopene has several notable characteristics that may confer potentially beneficial properties. Because lycopene is not converted to vitamin A, it may be entirely available for other properties (e.g., antioxidation). The lack of the β-ionone ring structure for lycopene may increase its antioxidant activity *(100)*. The stereochemical properties of lycopene are quite different from those of other commonly consumed carotenoids *(101)*, making it uniquely present in specific subcellular environments. Lycopene appears to be the most efficient quencher of singlet oxygen and free radicals among the common carotenoids *in vitro (8,102–104)*. In some populations, lycopene is the predominant carotenoid in plasma *(105–107)* and in various tissues *(108,109)*.

The unique biochemical properties of lycopene may render it able to protect cellular components against specific types of damage from highly reactive oxygen species. The source of the reactive compounds differs by tissue type and includes smoking, sunlight, chronic inflammation, and normal metabolic processes *(110–112)*. For example, smokers' lungs are exposed to high levels of nitric oxide (NO), which can react with oxygen to produce the $NO_2\cdot$ radical. NO_2 radicals survive for long enough in fresh smoke to reach lung tissue *(113)*. Lycopene is one of the

major carotenoids found in lung tissue, and concentrations vary widely among individuals *(114)*. Using an *in vitro* assay, Böhm et al. *(115)* showed that carotenoids are effective in protecting lymphocytes from NO_2 radical damage and that lycopene was at least twice as effective as β-carotene. Lycopene was shown to possess anticancer properties in a mouse lung carcinogenesis model *(96)*.

Chronic infection by *Helicobacter pylori* is a major established risk factor for gastric cancer. Chronic infections may increase cancer risk by increasing the oxidative load *(116)*. Elevated DNA oxidation occurs early during *H. pylori* infection *(117)*. Dietary antioxidants, including lycopene, may potentially reduce the impact of oxidative load from *H. pylori* infections in the stomach. Another potential contributing factor to stomach cancer is the endogenous formation of *N*-nitrosamines. Vitamin C has been considered to be an inhibitor of the nitrosation that generates *N*-nitrosamines. It is interesting that an ecologic study in Japan *(45)*, an area with a high incidence of stomach cancer, showed no association between average plasma vitamin C level and stomach cancer, and, in fact, the area with the lowest gastric cancer incidence had the lowest vitamin C level. In contrast, plasma lycopene level was associated with stomach cancer rate more so than the levels of other "antioxidant" nutrients assessed (vitamins A, C, and E and β-carotene) *(45)*. A study of determinants of endogenous generation of *N*-nitrosamine in rats *(118)* suggested that various aspects of food products may explain their inhibitory effect, including pH, and ascorbic acid, lycopene, and β-carotene contents. Tomato and tomato-based products are the predominant sources of lycopene and one of the major sources of ascorbic acid in some populations.

Reactive oxygen compounds may contribute to prostate carcinogenesis *(119,120)*. Prostate epithelial cells in many men at the age of risk for prostate cancer are likely to be exposed to inflammatory-related reactive oxygen species because of the high prevalence of prostatitis. However, whether an antioxidant property accounts for the apparent benefit of tomato product consumption on prostate cancer risk remains unproven.

If oxidation proves critical to carcinogenesis, the dietary contribution to antioxidation is likely to be immensely complex. Synergy among antioxidants exists in experimental systems *(121)*, and synergistic effects are likely to be more complex *in vivo*. For example, synergy between α-tocopherol and ascorbic acid is well established *(121)*, resulting from the ability of ascorbic acid to reduce α-tocopheroxyl radicals, thereby recycling α-tocopherol. Complex synergistic effects may occur as a result of such direct interactions (e.g., recycling), different abilities of antioxidants to scavenge the various reactive oxygen species thus enhancing overall protection *(103)*, and the localization of different antioxidants in diverse subcellular compartments. Possibly, the benefits of tomatoes may result from the complex interaction of various carotenoids, ascorbic acid, and other antioxidant polyphenolic compounds.

Although the notion that lycopene may exert its role in humans through limiting cellular macromolecule damage from reactive oxygen species is appealing, other mechanisms may be operative. In addition, preliminary *in vitro* evidence indicates that lycopene reduces cellular proliferation of various cancer cell lines induced by insulin-like growth factor-I (IGF-I) *(85)*. This finding, which requires confirmation, is intriguing, given recent evidence that the circulating level of IGF-I is positively associated with higher risk of various cancers, including prostate cancer *(122)*. Various other potential mechanisms have been postulated *(100,108,123,124)*. Most of the mechanistic data have been based on *in vitro* studies, but a recent study *(125)* found that supplementation with tomato products, as well as carrot and spinach products, resulted in a marked decrease in endogenous levels of strand breaks in lymphocyte DNA. More human studies are clearly needed.

Conclusions

Intake of tomatoes and tomato-based products and plasma levels of lycopene, a carotenoid found predominantly in tomatoes, have been relatively consistently associated with a lower risk of a variety of cancers. Evidence is strongest for cancers of the lung, stomach, and prostate gland and is suggestive for cancers of the cervix, breast, oral cavity, pancreas, colorectum, and esophagus. A large body of evidence also indicates that other fruits and vegetables may have additional or complementary benefits *(3–5)*. The likelihood that the associations between increased consumption of tomato and tomato-based products and lower risk for several cancer sites are causal is supported by the consistency of evidence by study design (ecologic, case–control, and prospective) and by exposure assessment (dietary-based and plasma-based) and by the unlikelihood that biases or uncontrolled confounding could plausibly account for all these associations in diverse populations. These findings add further support to current dietary recommendations to increase consumption of fruits and vegetables to reduce cancer risk.

The benefits of tomatoes and tomato products are often attributed to the carotenoid lycopene. However, a direct benefit of lycopene has not been proven, and other compounds in tomatoes alone or interacting with lycopene may be important. It is critical to recognize that the current evidence regarding dietary intake and lycopene blood concentrations reflects consumption of tomatoes and tomato products rather than purified lycopene supplements. The pharmacokinetic properties of lycopene remain poorly understood, and it is premature to recommend use of pharmacologic doses of lycopene for any health benefit. Further research on the bioavailability, pharmacology, and biology of this potentially important carotenoid is clearly warranted. Until more definitive data regarding specific benefits of purified forms of lycopene are available, current recommendations should emphasize the health benefits of diets rich in a variety of fruits and vegetables, including tomatoes and tomato-based products.

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NOTES

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