

Promises and Perils of Lycopene/Tomato Supplementation and Cancer Prevention

Tomato Products, Lycopene, and Prostate Cancer: A Review of the Epidemiological Literature¹

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EXPANDED ABSTRACT

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In the past several years, 2 general lines of evidence have supported a role of lycopene in the prevention of certain malignancies, especially prostate cancer. First, important antioxidant properties of lycopene have been established (1). Given the relatively high concentrations of lycopene in the serum of many individuals and the potential role of oxidative stress in the formation or the progression of cancers, a potential anticancer influence of lycopene has been hypothesized. Second, a number of epidemiological studies have suggested that individuals with a relatively high intake of lycopene, particularly from tomato products, have a lower risk of prostate cancer (2). However, the association between tomato products or lycopene and lower prostate cancer risk, while suggestive, remains controversial, because not all the studies are supportive. The results from the epidemiological studies will be summarized here, and factors that may contribute to the apparent inconsistencies will be considered.

There have been 2 basic study designs, those based on dietary intakes and those based on plasma or serum measures of lycopene. The dietary-based studies have been either retrospective (case control), in which prior recalled diet in men with prostate cancer is compared with that of a control or a comparison group free of prostate cancer, or prospective (cohort), in which diet is assessed in men initially free of cancer who are then followed for the occurrence of prostate cancer. The dietary studies have either been based on tomato or

tomato-product intake or have estimated lycopene intake based on the intake of lycopene-containing foods.

Results from a recent meta-analysis serve as a useful starting point in summarizing the results. This meta-analysis summarized results from studies published up to March 2003 (3). The authors identified 11 case-control studies and 10 cohort studies or nested case-control studies that presented data on the use of tomato, tomato products, or lycopene, and that met the inclusion criteria. The main findings were that, compared with nonfrequent users of tomato products (1st quartile of intake), the relative risk (RR) of prostate cancer among consumers of high amounts of raw tomato (5th quintile of intake) was 0.89 (95% CI 0.80–1.00). For a high intake of cooked tomato products, the corresponding RR was 0.81 (95% CI 0.71–0.92). The RR of prostate cancer related to an intake of 1 serving/d of raw tomato (200 g) was 0.97 (95% CI 0.85–1.10) for the case-control studies and 0.78 (95% CI 0.66–0.92) for cohort studies. For serum- or plasma-based studies, the corresponding RRs were 0.74 (95% CI 0.59–0.92) for all studies, 0.55 (95% CI 0.32–0.94) for case-control studies, and 0.78 (95% CI 0.61–1.00) for cohort studies.

The meta-analysis indicates that results from cohort studies and serum- or plasma-based studies support about a 25–30% reduction in the risk of prostate cancer. The dietary-based case-control studies are generally not supportive, although 2 case-control studies that measured serum lycopene concentrations did find an inverse association with risk (3). Of 11 cohort studies of either diet or plasma, only 2 are nonsupportive. One of these studies, conducted in The Netherlands (4), found no appreciable association between tomato consumption and prostate-cancer risk. However, tomato consumption appeared to be low in this population. In the positive studies conducted in the United States, the average intake of lycopene may have exceeded that in the Dutch study by about 10-fold. The other null cohort study was a study of prediagnostic serum carotenoids and prostate-cancer risk conducted between 1971 and 1993 in a Japanese-American population in Hawaii (5). In that study, a single assessment of serum lycopene was used to

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characterize follow-up for up to a 22-y period, with only 14 cases occurring within the first 5 y of follow-up. The serum lycopene levels were quite low. The median serum concentration among controls was only 250 nmol/L compared with 597 nmol/L in the Hsing et al. study (6) and 791 nmol/L in the sample of 121 health professionals (7) and 724 nmol/L in the Physicians' Health Study (8). Thus, in these 2 null studies, the intake of lycopene-rich products was probably far less than in the 9 studies suggesting an association.

Assessment of diet in epidemiological studies is, in general, complicated, but there are specific complexities in the assessment of lycopene. First, lycopene is in a number of food items, many of which are not systematically assessed in current questionnaires. These may include tomatoes, salads, soups, pizza, mixed dishes, salsas, ketchup, and juices, and also in some nontomato items (e.g., watermelon, pink grapefruit). Second, particularly given the complexity of many of the items, it is unclear how valid the current nutrient databases are. Third, bioavailability is quite important and may vary profoundly across different food items. For bioavailable lycopene, measurement error is likely to be substantial in many studies. In studies that have compared dietary lycopene intake with circulating levels (9–11), correlations have generally been about 0.2. Thermal processing disrupts lycopene from binding matrices, and incorporation into an oil base makes this highly lipophilic compound available to micelles, a necessity for intestinal absorption. In some studies, the more bioavailable sources of lycopene appeared to be more strongly related to a lower risk of prostate cancer. Measurement error, if random between cases and controls, would suggest that the observed associations actually underestimate the potential full benefit of lycopene or tomato products.

As in any observational studies, the most important remaining issue regarding the relation between tomato products or lycopene with prostate cancer is whether this is merely a marker or is a truly causal protective factor. In most studies, controlling for dietary variables did not alter the association. However, in one case-control study (12), a suggestive inverse association observed for cooked tomatoes [RR (adjusted for covariates) = 0.73 (95% CI = 0.48–1.10) for 3 vs. <1 serving per wk; *P* (2-sided) for trend = 0.13] was attenuated when it was additionally controlled for total fruits or vegetables (RR = 0.90). In contrast, in a larger cohort study (13), controlling for fruit and vegetable intake or for olive oil use (a surrogate of a beneficial Mediterranean dietary pattern) did not change an apparent protective association with tomato products. Moreover, total fruit and vegetable intake has not been generally related to prostate-cancer risk nor to lycopene level (14–16), therefore it is unlikely to be a major confounder.

Tomato product intake has also been associated with a reduced risk of several other cancer sites, particularly malignancies of the lung and the stomach (2). However, attributing the apparent protective association to lycopene or to tomato products is problematic, because these results are limited almost entirely to dietary-based case-control studies, and, for the most part, it is unclear whether this potential benefit was separated from a potential benefit of total fruits and vegetables. Moreover, there are almost no prospective studies or serum-

based studies. Thus, while further study is warranted, it is premature to attribute potential benefits uniquely to tomato products, let alone to lycopene.

CONCLUSIONS

Future epidemiological studies, to be maximally informative, should 1) examine populations with relatively high intakes of tomato products; 2) be sufficiently large to evaluate moderate relative risks; 3) have a comprehensive assessment of major lycopene sources; 4) account for bioavailability of lycopene; 5) account for temporal patterns, because a single dietary or blood assessment, particularly in studies with long follow-up periods, may be inadequate; and 6) examine if a benefit of tomato products or lycopene is modified by genetic polymorphisms in relevant genes (e.g., DNA repair genes). Intervention studies with appropriate intermediate markers may also be informative.

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