Invited Commentary: Tomatoes, Lycopene, and Prostate Cancer. How Strong Is the Evidence?

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Until only recently, there was little evidence that intakes of fruits and vegetables were related to prostate cancer risk. Findings from observational epidemiologic studies were weak and inconsistent, and the results from three large randomized clinical trials of supplemental β-carotene (an antioxidant carotenoid found primarily in yellow and orange vegetables) showed no effects on prostate cancer (1–3). In 1995, Giovannucci et al. reported a 35 percent reduced prostate cancer risk, comparing men who ate more than 10 weekly servings of tomato products with those who ate fewer than 1.5 servings weekly (4). They suggested that this effect might be attributable to lycopene, the antioxidant carotenoid found primarily in tomatoes. This result motivated heightened interest in lycopene and prostate cancer; subsequent scientific reports, including those by Freeman et al. (5) and Norrish et al. (6) in this issue of the Journal, provide additional insight into the associations of fruits and vegetables with prostate cancer risk. In this commentary, we give a very brief summary of this literature, make recommendations for further research, and present our perspective regarding the strength and coherence of the hypothesized protective effect of tomato products on prostate cancer risk.

There is a large and quite variable literature on the associations of fruit and vegetable intakes with prostate cancer risk. Only eight studies examined total fruit and/or vegetable intakes (7–14), and only one found a significant protective association (11). We could find 17 studies that examined specific fruits and/or vegetables. Individual studies have found protective effects for beans, lentils, peas, carrots, greens, tomatoes, one or more cruciferous vegetables, tofu, dried fruit, nuts, apples, pears, and citrus fruits, but there is no consistent evidence for any particular vegetable compared with another (4, 7, 9–11, 15–25). Of the 17 studies that have examined dietary carotenoid intake (4, 7, 9–11, 21, 24, 26–35), two found protective effects for β-carotene (24, 29) and one found a protective effect for lycopene (4). Finally, of the five studies of serum carotenoids (36–40), one found a protective effect for lycopene (40). Limitations of many of these studies include small sample sizes, incomplete dietary assessment, and lack of control for important confounding variables. It is challenging to synthesize the results of this research into a compelling statement on the association of fruits and vegetables, or any specific component of fruits and vegetables, with prostate cancer risk.

Seven studies now address whether tomato products reduce prostate cancer risk. Of the seven studies of diet, three found significant negative associations (4, 14, 22), the new report by Norrish et al. (6) is inconclusive, and three found no association (16, 24, 25). Of the studies examining prediagnostic serum lycopene concentration, one found a negative association (40) and two found no association (36, 38). One of the difficulties in interpreting this literature is that few studies, prior to the report by Giovannucci et al. in 1995 (4), examined tomato products or lycopene comprehensively, and the paucity of null results in earlier studies could be due to publication bias.

The two studies in this issue of the Journal (5, 6) add some useful insights into the questions of lycopene and prostate cancer risk. One important question is whether carotenoid concentrations in prostate tissue are in relative proportions to those found in serum or whether there is a preferential concentration of certain carotenoids, as there is for lutein and zeaxanthin in the macular pigment (41). A previous study by Clinton et al. (42) found levels of lycopene in prostate tissues that were on average 31 percent higher than levels of β-carotene and at least twofold greater than levels of each of the other major carotenoids. Tissue and serum levels were not compared. In contrast, Freeman et al. (5) found concentra-
Tons of lycopene equal to those of β-carotene and 35 percent lower than those for lutein. Furthermore, serum concentrations of all carotenoids (and tocopherols) were similarly and significantly correlated with prostate tissue levels, and relative proportions of each carotenoid in prostate tissue matched well with their proportions in serum. These results suggest that there is no preferential concentration of lycopene in the prostate, rather that levels of prostate carotenoids (and tocopherols) reflect passive uptake from the serum lipoproteins in which they are transported.

Unfortunately, the report by Freeman et al. (5) does not well address the question of whether dietary variability affects prostate carotenoid concentrations. Determinants of serum carotenoids are complex (43); given the limits of dietary assessment methods (44), the modest reliability of any single measure of serum carotenoids (44), and the interactions of other dietary constituents and lifestyle factors that affect carotenoid absorption (45), expected correlations between diet and serum carotenoids are small. In addition, accurate analytical data on the lycopene content of cooked tomato products, first published in 1995 (46) and not incorporated into comprehensive nutrient databases until 1998 (47), were not used in this study. Both observational studies and feeding studies have demonstrated associations of dietary carotenoid intakes with their serum concentrations (48). Either large sample sizes and improved dietary assessment methods or well-designed feeding trials will be necessary before associations between diet and prostate tissue levels can be demonstrated.

A second issue, addressed by Norrish et al. (6), is the importance of designing studies with an a priori hypothesis identifying tomato products as an exposure of interest. Food frequency questionnaires, the only practical dietary measure for large epidemiologic studies, offer the opportunity to examine a very large number of individual foods, food groups, nutrients, and the ratios among them. There will necessarily be statistically significant associations due to chance alone, which can best be explored in independent studies designed to address the hypothesis of interest. To this end, the study by Norrish et al. included a comprehensive instrument to measure consumption of tomato products. A nonsignificant trend of decreasing risk was associated with increased consumption of tomato products, and associations with lycopene were neither statistically significant nor monotonically ordered across levels of intake.

There are, however, two limitations of the study by Norrish et al. (6) that make the results difficult to interpret. First, the summary variable for consumption of all tomato-containing foods was categorized in total grams per day. Much variability exists in serving weights across these diverse foods (e.g., tomato sauce vs. tomato soup); thus, this approach to categorization may not well capture the exposure of interest. Second, a 1993 nutrient database was used to calculate lycopene intake (49); more recent analyses have found the lycopene content of foods made with prepared tomato products such as tomato paste to be as much as 10 times higher than originally estimated (46). It is unclear whether a more accurate nutrient database would have affected these results. Nevertheless, this study gives little support for the hypothesized protective effect of tomato products and lycopene on development of prostate cancer.

We offer three suggestions for improving observational studies on tomato products, lycopene, and prostate cancer. First, it is necessary to separate the effects of vegetables in general from tomato products specifically. One analytical approach would be to report the effects of increasing intakes of several classes of vegetables, including tomato products, both with and without control for total servings of vegetables. By controlling for total vegetable intake, the statistical model would examine the effects of substituting one type of vegetable for other types of vegetables while keeping total vegetable intake constant. This would be a much stronger test for the effect of a specific vegetable than would models that examine each vegetable group independently. Also remember that in many populations, lycopene is the primary carotenoid in both the diet and serum. For example, in one population-based study in the United States, the mean (standard deviation) serum lycopene concentration was 0.58 (0.40) μmol/liter, followed by 0.22 (0.10) μmol/liter for lutein and 0.18 (0.15) μmol/liter for β-carotene (43). In some studies, lycopene may simply be the best marker of vegetable intake in general or may be a marker of some other, correlated dietary or lifestyle factor.

Second, we must develop dietary questionnaires and associated nutrient databases that are sensitive to the foods and nutrients of interest. Correlations of dietary with serum lycopene tend to be smaller than correlations between diet and serum for other carotenoids (48), suggesting much need for improved dietary instrumentation. Standard food frequency questionnaires do not well capture many concentrated sources of lycopene, which are found dispersed throughout the diet in sauces, condiments, and multiple-component foods such as casseroles. In addition, these questionnaires are not particularly sensitive to lycopene bioavailability, which is markedly increased by heat processing and consumption with fat (50, 51). Furthermore, nutrient databases with updated...
carotenoid values are now available and should be incorporated into future studies.

Third, new studies on diet and prostate cancer must consider some unique confounding factors beyond social and demographic characteristics. Most importantly, analyses must address the complex associations between use of prostate-specific antigen (PSA) screening, the likelihood of cancer detection, and health-related behavior. In a recently completed population-based case-control study of prostate cancer risk, we found a relative risk of 7.5 comparing men who had received five or more PSA screening tests in the previous 5 years with those who had received none (52). Men who receive PSA screening are also more likely to be better educated, practice healthful dietary behavior, and use dietary supplements (53). Thus, associations of healthful diets will appear weaker (or could conceivably be reversed in direction) because the likelihood of cancer detection is correlated with the hypothesized protective behavior. This may be one reason that the reports of Giovannucci et al. (4) and Gann et al. (40) found strong associations of lycopene with advanced-stage disease only, where confounding by PSA screening would be less likely. In addition, it is probably also necessary to control for dietary supplement use. Four studies have found effects of dietary supplements on prostate cancer risk (51–54), and users of dietary supplements are more likely to eat healthful diets and to receive PSA screening (54).

Our view is that, to date, evidence that tomato products are associated with a reduced risk of prostate cancer is inconclusive. A good benchmark for interpreting present studies on lycopene and prostate cancer is to remember the far more comprehensive and consistent body of evidence linking β-carotene to reduced lung cancer risk. For lung cancer, case-control and prospective studies have shown that higher serum β-carotene concentration is similar to other components of high-carotenoid vegetables. We should also consider that the list of dietary factors associated with prostate cancer has become quite long, including fat and specific fatty acids, soy, calcium, various vegetables, lycopene, and supplements of vitamin E, selenium, vitamin C, and zinc (56). Further observational research, using comprehensive diet assessment methods and appropriate statistical models followed by clinical trials, will be needed to identify those dietary patterns that could reduce the burden of prostate cancer.

REFERENCES