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Lycopene and prostate cancer risk. Methodological considerations in the epidemiologic literature*

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Abstract: Prostate cancer is the most common cancer in U.S. males. Among potentially beneficial natural compounds is lycopene, which is derived largely from tomato-based products. Recent epidemiologic studies have suggested a potential benefit of this carotenoid against risk of prostate cancer, but not all of the studies have been supportive. The largest prospective dietary study, the Health Professionals Follow-Up Study (HPFS), had found that 2–4 servings of tomato sauce per week were associated with about a 35 % risk reduction of total prostate cancer and a 50 % reduction of advanced prostate cancer in follow-up from 1986 to 1992. Tomato sauce was by far the strongest predictor of plasma lycopene levels in this study. In the largest plasma-based study, high lycopene levels were associated with similar risk reductions for total and advanced prostate cancer. Results from other studies, mostly dietary case-control studies, have been mixed. The reasons for these inconsistencies are unclear. Because lycopene may come from a number of sources, and the bioavailability of lycopene may vary profoundly across these sources, dietary questionnaires are likely to vary markedly in their utility to estimate true variation in body lycopene stores across individuals. With further follow-up in the HPFS, we addressed some possibilities for apparently conflicting results. We confirmed our initial findings with the independent 1992–1998 follow-up period. Our results also indicated various factors may contribute to some of the inconsistencies, including insufficient sample size, low intake of lycopene, failure to account for bioavailability, reliance on a single dietary assessment, and heterogeneity of prostate cancer.

INTRODUCTION

In the past several years, two lines of emerging evidence have supported a role for lycopene in the prevention of certain malignancies, especially prostate cancer. First, antioxidant properties of lycopene have been established [1]. Given the relatively high concentrations of lycopene in the tissues of many individuals, and the potential role of oxidative stress in the formation or progression of cancers, a potential anticancer influence of lycopene has been hypothesized. Secondly, a number of epidemiologic studies have suggested that individuals with 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 of the

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studies are supportive. This review summarizes the epidemiologic studies, and discusses methodological factors that may contribute to the apparent inconsistencies.

There have been two basic types of study designs, those based on dietary intakes and those 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 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.

CASE-CONTROL STUDIES

The first study that reported on tomato intake and prostate cancer risk was a case-control study of prostate cancer conducted in Minnesota [3]. The investigators reported that high consumers of tomatoes (>14 times per month) had about a 30 % lower risk of total prostate cancer than low consumers (<3 times per month), although the results were not statistically significant. Another case-control study, conducted in a multi-ethnic population in Hawaii [4], found no association between intake of tomatoes and prostate cancer risk. However, the actual intakes and the specific items assessed were not reported, and tomato-based products such as tomato sauce may not have been specifically considered in that study.

Three recently published case-control studies conducted in the United States have examined dietary lycopene and tomato intake in relation to prostate cancer risk. One study [5] did not find statistically significant associations with either total or advanced prostate cancer for various components of tomato products, although raw (but not cooked) tomatoes were suggestively associated with lower risk of advanced prostate cancer [relative risk (RR) = 0.5 for top versus bottom category; p (trend) = 0.05]. In contrast, tomato juice was related to higher risk of prostate cancer for white men [RR = 2.8; p (trend) = 0.02], but not black men.

A large multi-ethnic case-control study of prostate cancer [6] overall did not support a benefit of tomatoes or lycopene. However, among black men, an inverse association between risk of prostate cancer and cooked tomatoes intake was suggested [RR = 0.72; 95 % confidence interval (CI) = 0.41–1.26, between high and low tertiles]; however, the corresponding associations for white men (RR = 0.90; 95 % CI = 0.54–1.51) and Japanese men (RR = 0.85; 95 % CI = 0.20–3.65) were weak. Chinese men, the other ethnic group in the study, ate amounts of cooked tomato products that were too low to provide informative data.

A study conducted in Seattle [7], restricted to men under the age of 65, found neither cooked tomatoes nor uncooked tomatoes were appreciably correlated with risk of prostate cancer. While 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 vs. <1 serving per week]; this association was largely attenuated when total fruits or vegetables were additionally controlled for (RR = 0.90). The authors concluded that a modest association between tomato product intake and prostate cancer may exist, but this association may not be specific to tomatoes, but rather vegetables in general.

Four case-control studies based outside the United States have examined this hypothesis. A case-control study conducted in the United Kingdom [8] reported no association between raw or cooked tomatoes and risk of prostate cancer. Interestingly, the strongest association found in that study was for baked beans (RR = 0.52; 95 % CI = 0.31–0.88, for high versus low intake). The authors of that study speculated that tinned baked beans, which are usually stored in tomato sauce, may possibly be the best source of highly bioavailable lycopene in this population, although this supposition was not directly assessed. A study conducted in Greece [9] found that men with prostate cancer reported slightly fewer raw tomatoes (p = 0.12) but significantly fewer cooked tomatoes (p = 0.005). This association was observed only in men over the age of 70 years [10]. A Canadian study [11] did not find an association

for total prostate cancer with lycopene intake, but did report a significant inverse association with tomato items. Results were not reported separately for subclassifications of tomato items (e.g. cooked, processed, raw). A study in New Zealand [12] 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). Intakes of tomato and tomato-based foods accounted for this modest association, but raw tomatoes were not associated with risk of prostate cancer.

PROSPECTIVE STUDIES

Four prospective dietary-based studies [13–16] have reported on the relationship between tomato or lycopene consumption and prostate cancer risk. The first report was from a study conducted in 14 000 Seventh-Day Adventist men [13]. In that study, men with higher intakes of tomatoes had a lower risk of prostate cancer in a multivariate analysis. The only other food items related to a lower prostate cancer risk were beans, lentils, and peas.

The largest study to date was conducted in almost 50 000 male health professionals living in the United States [15]. The first report from this study was based on follow-up from 1986 to 1992 and on 773 cases of prostate cancer. Intakes of beta-carotene, alpha-carotene, lutein, and beta-cryptoxanthin were not associated with risk of prostate cancer, but high intake of lycopene was associated with a 21 % reduced risk of prostate cancer. Also, high intake of tomatoes and tomato products was associated with a 35 % lower risk of total, and a 53 % lower risk of metastatic prostate cancer. Tomato sauce (2–4 servings/week) had the strongest inverse association with prostate cancer risk among all food items assessed (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. Recently, results based on 2481 cases and updated dietary measures from 1986 to 1998 were reported from this cohort [17]. For tomato sauce intake, the strongest predictor of plasma lycopene, men with higher intakes were at reduced risk of prostate cancer from 1992–1998 [RR = 0.79; 95 % CI = 0.64–0.97 for 2+ servings/week vs. <1 serving/month; p (two-sided) for trend = 0.0006]. This result confirmed the earlier report.

A cohort study conducted in the Netherlands [16] found no appreciable association between tomato consumption and prostate cancer risk. However, tomato consumption appeared to be low in this population. Also, processed or cooked tomato products may not have been explicitly addressed. Preliminary results from another cohort study [14] also support approximately 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 [18–20] have reported on the risk between prediagnostic serum or plasma concentrations of carotenoids and risk of prostate cancer. These studies assessed frozen prediagnostic serum or plasma samples that were collected in large groups of men who subsequently were followed for incidence of prostate cancer. Concentrations of carotenoids were then compared to those from a random sample of men from the cohort who did not develop prostate cancer in the corresponding time period. An additional study collected samples after the diagnosis of prostate cancer in 65 men and compared carotenoid levels to 132 cancer-free controls [21]. This study found a markedly lower odds ratio with higher concentrations of lycopene (0.17, comparing high vs. low quartiles; $p = 0.005$). However, other carotenoids, including zeaxanthin, lutein, and beta-cryptoxanthin, were also related to lower risk. Because samples were collected after the diagnosis of prostate cancer, these results should be viewed with particular caution because the direction of the causation is less clear.

The first published report using prospective data [18], based on serum obtained in 1974 from 25 802 persons in Washington County, Maryland, found a 6.2 % lower median lycopene level in men with prostate cancer diagnosed during a 13-year period compared to age- and race-matched controls.

The relative risk was 0.50 (95 % CI = 0.20–1.29) between high and low quartiles of lycopene. Other carotenoids were not associated with lower prostate cancer risk.

This study was followed by a larger blood-based study with approximately six times the number of cases from the Physicians' Health Study (PHS) [19]. Using samples stored in 1982, 578 prostate cancer cases were diagnosed over the next 13 years. Of these cases, 259 were classified as "aggressive", defined by high grade or advanced stage. A lower risk of prostate cancer, particularly for aggressive prostate cancer was observed (RR = 0.56; 95 % CI = 0.34–0.92) when comparing high to low quintile of plasma lycopene. None of the other carotenoids measured in this study were related to risk of prostate cancer. Because this study population was derived from a randomized trial of beta-carotene, analyses were further stratified by beta-carotene or placebo assignment; the inverse association with lycopene was primarily observed among men who had received placebo. In contrast, results were weak for those randomized to receive beta-carotene, suggesting men with low levels of beta-carotene may benefit more by lycopene.

A study of prediagnostic serum carotenoids and prostate cancer risk, conducted between 1971 and 1993 in a Japanese-American population in Hawaii [20], did not find an association between serum lycopene levels and risk of prostate cancer. In that study, a single assessment of serum lycopene was used, and its follow-up period was 22 years. The study included "low-virulence" prostate cancer (28 % were diagnosed incidentally during surgery for benign prostatic hyperplasia) in a low-risk population. Moreover, the serum lycopene levels were quite low compared to other studies, the median serum concentration among controls was only 134 ng/ml, compared to 320 ng/ml in the Washington County study [18], 424 ng/ml in a sample of 121 men from the HPFS [15], and 388 ng/ml in the PHS [19].

ASSESSMENT OF EXPOSURE (DIETARY INTAKE OR BLOOD LEVEL) IN EPIDEMIOLOGIC STUDIES

Assessment of dietary intakes in epidemiologic studies is difficult in general, but specific complexities exist for the assessment of lycopene. First, lycopene is found in a number of food items, many of which are not systematically assessed in current questionnaires. These items may include tomatoes, salads, soups, pizza, mixed dishes, salsas, ketchup, and juices. Also, some non-tomato items (e.g., watermelon, pink grapefruit) contain lycopene. Secondly, the validity of the current nutrient databases for lycopene is not well established for these diverse items. Thirdly, bioavailability of lycopene may vary profoundly across different food items, which contributes to measurement error. Thermal processing disrupts lycopene from its binding matrices, and lipids make this highly lipophilic molecule available to micelles required for intestinal absorption. This may explain why in some studies, associations were stronger for cooked tomatoes. In studies that have compared dietary lycopene intake with circulating levels [22–32], correlations have generally been about 0.2, with the highest being 0.46 [30]. These generally low correlations demonstrate the difficulties of adequately assessing bioavailable lycopene through questionnaires.

TIMING OF DIETARY OR BIOMARKER MEASURES IN RELATION TO RISK OF DISEASE

The time period of risk wherein intake of lycopene is most likely to be relevant is currently unknown. Since prostate carcinogenesis takes decades, lycopene intake can possibly be important early or late in the process. An important issue is the ability of various studies to assess lycopene intake at various points in life in relation to the period of risk. Only one study [17] had the ability to examine intake at various time points prior to the diagnosis, and this study suggested that more recent intake (approximately within 5 years of the diagnosis) may have been most important. In that study, with 12 years of follow-up, if dietary information had not been updated periodically, the inverse association initially observed would have been markedly attenuated over time. This finding is also supported by analyses in

the PHS [19], which found that risk was stronger initially after the blood collection and tended to weaken over time. In contrast, in a Japanese-American population in Hawaii [20], which did not find an association between serum lycopene levels and risk of prostate cancer, a single assessment of serum lycopene was used to characterize follow-up for up to a 22-year period, with the vast majority of cases occurring after the first 5 years of follow-up. More data are needed, but the limited evidence currently suggests that relatively recent exposure is most important.

AGE AT DIAGNOSIS

One study that explored whether the magnitude of risk factors for prostate cancer varied by age found a strong inverse association between cooked tomato intake and prostate cancer risk in men over the age of 70 years, but not for younger men [10]. In that study, higher intake of cooked tomatoes was associated with a lower risk among men ≥70 years (RR = 0.29; 95 % CI = 0.14–0.59) but not those <70 years (RR = 1.14; 95 % CI = 0.54–2.40). In a recent analysis of male health professionals, a similar pattern was observed [17]; an inverse association with tomato sauce intake was weak, if at all present, for men under the age of 65 years when diagnosed (RR = 0.89; 95 % CI = 0.67–1.17; p for trend = 0.20; n = 807 cases) and strong for men 65 years or older (RR = 0.69; 95 % CI = 0.56–0.84; p for trend = 0.001; n = 1674 cases). In this regard, it is interesting that a case-control study that did not support the hypothesis [7] was restricted to men under the age of 65. Possibly, prostate cancers presenting at an early age may represent an accelerated process of carcinogenesis that is influenced more by genetic or endogenous factors and perhaps other exogenous factors, whereas older onset prostate cancer may be more related to lycopene. Of note, the vast majority of prostate cancer deaths occur in mean over the age of 65 years.

DETECTION BIAS

From an epidemiologic perspective, prostate cancer is quite difficult to study because of profound heterogeneity in the biologic potential of the disease. Moreover, in recent years, prostatic-specific antigen (PSA) screening has become widespread in the United States, with two potential consequences. First, many lesions of questionable clinical importance are detected, and secondly, potential for detection bias is substantial because many cancers are diagnosed primarily as a result of screening. Thus, if an exposure of interest (e.g., diet) is related to screening behavior, a spurious association between the exposure and the diagnosis of prostate cancer may occur. One study took PSA screening into account, and the inverse association with tomato products appeared to exist for both PSA-detected early-stage lesions and highly aggressive metastatic cancers that were detected clinically [17]. These findings would suggest that lycopene influences a range of prostate cancers. Future studies need to take frequency of PSA screening into account.

CONFOUNDING FACTORS

Although an inverse association between intake of tomato products or lycopene or circulating levels of lycopene has been observed in a number (though not all studies), these studies are observational in nature. Because the exposure was not randomized, the possibility remains that another causal protective factor correlated with tomato or lycopene intake is the actual etiologic factor. There are two relevant questions: first, whether the etiologic factor is truly from tomato products, and secondly, if so, whether lycopene is the active component. Although neither can be answered definitely at this time, the existing body of evidence can be examined for clues to determine the likelihood that a confounder accounts for this association.

The first consideration is whether the association observed with tomato products in the positive studies was related to another factor. In general, multivariate analyses indicated no appreciable con-

founding between lycopene or tomato product intake and prostate cancer risk. The potentially confounding variables assessed in at least some of the studies included other dietary factors, body mass index, aspirin use, marital status, ancestry, level of physical activity, vasectomy, smoking habits, and alcohol. One case-control study merits particular consideration [7] because a suggestive inverse association was observed for cooked tomatoes, RR (adjusted for covariates) = 0.73 (95 % CI = 0.48–1.10) for ≥3 vs. <1 serving per week, but this inverse association was attenuated when additionally controlled for total fruits or vegetables (RR = 0.90). This led the authors [7] to conclude that in previous studies, tomato products or serum lycopene levels may have been confounded by intake of total fruits and vegetables. However, this explanation does not appear likely because (1) total fruit and vegetable intake has not been related to prostate cancer risk in general, (2) in the largest study [17], fruit and vegetable consumption did not confound the results, and (3) total fruit and vegetable intake has not been appreciably related to lycopene level [24,30,32]. The potential for confounding is related to the magnitude that a potential confounding factor is related to the exposure of interest (i.e., lycopene intake or level) and to the outcome. Overall, fruits and vegetables are very weakly, if at all related to lycopene level and to prostate cancer risk.

One study also considered whether tomato consumption was acting as a surrogate of a beneficial Mediterranean dietary pattern [17]. While an inverse association with prostate cancer was seen in that study for tomato sauce among men of Southern European ancestry, an inverse association was also observed among men of other Caucasian ancestry. In addition, controlling for olive oil as "usual type of cooking oil" to examine further whether tomato sauce was part of Mediterranean dietary pattern did not change the inverse association between tomato sauce intake and prostate cancer risk

Thus, overall the epidemiologic literature tends to support a specific benefit of tomato products. Whether this apparent benefit is related solely to lycopene is much more difficult to evaluate. Tending to support a specific role of lycopene is the finding in some studies that among all tomato products, those that are better sources of bioavailable lycopene tend to be more strongly related to lower risk [5,9,12,15,17]. However, the possibility that other components (including other carotenoids) with similar bioavailability properties of lycopene account for the benefit cannot be excluded.

SUMMARY AND CONCLUSIONS

Most studies that have examined tomato product or lycopene intake or circulating lycopene levels in relation to prostate cancer risk support a statistically significant inverse association [9,13–15,17,19,21] or are consistent with approximately a 30 % reduction in risk (though not statistically significant) [3,12,18]. However, a number of studies are nonsupportive [4–8,16,20], although in at least three of the nonsupportive studies [4,16,20], intake of tomato products or sources of bioavailable lycopene may have been too low.

Given that the association is likely to be moderate in magnitude (approximately a 30 to 40 % reduction in risk), it is impressive that most studies support this hypothesis. The following reasons would contribute to weaken real associations: (1) populations with relatively low intakes of tomato products; (2) studies too small to evaluate moderate-sized relative risks; (3) non-comprehensive assessment of major lycopene sources; (4) not accounting for bioavailability of lycopene; (5) not accounting for temporal patterns, particularly in studies with a single dietary or blood assessment and long follow-up periods; and (6) heterogeneity in prostate cancer, such as different risk factors by age groups. Some evidence suggests that each of these factors may have tended to attenuate potential associations in at least some of the "null" studies. To be maximally informative, future epidemiologic studies in this area should attempt to address these important methodological issues.

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