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Lycopene, tomato products, and prostate cancer prevention. Have we established causality?*

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Abstract: The relationship between tomato products and prostate cancer prevention has been the subject of increasingly intense research activity over the past decade. The hypothesis that tomato products contain phytochemicals, perhaps lycopene and others, that modify prostate carcinogenesis warrants investigation. However, scientists, regulatory agencies, marketers of products, and those defining public health policy have differing opinions regarding the strength of the data when applied to criteria for inference and causality. It is useful to briefly review these criteria and discuss the relative strengths and weaknesses of the published data in order to better define future directions for research. Accepted categories of criteria include: consistency, strength of association, biological gradient, temporality, specificity, biological mechanisms and coherence, and experimental evidence. We believe that continued support for research regarding tomato products, lycopene and other phytochemicals, and prostate cancer risk is warranted and may ultimately serve as the basis for more consistent public health recommendations for the consumer. But, what do we say to the public when the data is still inconclusive? The authors support the recommendation that a minimum of five servings of fruit and vegetables should be consumed daily from a variety of sources. We believe that the hypothesized benefits of tomato products for prostate cancer prevention may be achieved with approximately five servings of tomato products per week. The consumption of lycopene supplements is not currently recommended for prostate cancer prevention or therapy. Future research will allow us to provide more definitive guidelines.

INTRODUCTION

The public and the biomedical community are increasingly aware of associations between tomato products, lycopene, and health outcomes. Scientists from many disciplines ranging from epidemiology, clinical medicine, nutrition, agriculture, and molecular and cell biology have published peer-reviewed studies providing intriguing data suggesting that tomato products and the carotenoid lycopene may be involved in cancer prevention, reducing the risk of cardiovascular disease, and limiting the morbidity or

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mortality of other chronic diseases. Unfortunately, the scientific data is often misinterpreted or overstated by the popular press as well as by purveyors of alternative dietary supplements and by some in the food industry. Advertisements for lycopene-containing products are now common around the globe.

The area of particular interest to our laboratory is the hypothesis that tomato products or lycopene may prevent or slow the progression of prostate cancer. Over the past decade, data has gradually accumulated evaluating this relationship. Many scientists, and certainly the public, are unaware that methodology and criteria for establishing causality have evolved over several decades in the public health literature and have been employed to address relationships between environmental factors and cancer risk in order to define public policy [1]. It is reasonable to examine some of these criteria and briefly review them in context of tomato products, lycopene, and prostate cancer risk.

WHAT IS CAUSALITY?

Causality can be defined as a specific occurrence or outcome that is consistently preceded by a known set of circumstances or conditions. To determine causality, we must be able to make conclusions about the occurrence of an event and have scientific knowledge regarding the reasons for the occurrence. In nutritional sciences, causality has been determined for many nutrient-deficiency diseases. For example, the high incidence of scurvy among British sailors in the 1700s led to primitive scientific studies showing that diets devoid of citrus fruits for long periods of time resulted in scurvy and that inclusion of specific foods in the diet effectively prevented the disease. Decades of research ultimately led to the conclusion that vitamin C deficiency was the cause of scurvy and that pure ascorbic acid would effectively prevent the deficiency syndrome [2]. Similar knowledge for a vast array of essential vitamins and minerals ultimately led to public health guidelines in the form of recommended dietary allowances (RDAs) [2]. Another example where causality criteria have been applied for the development of public health policy concerns the relationship between tobacco smoking and cancer risk [3]. Inference and causality is often not as clear as illustrated by these examples. Many cancers and chronic diseases have a complex and multifactorial etiology. Furthermore, ethical, economic, and political considerations often influence public policy. For example, the costs, risks, and benefits of mammography for women in different age groups remains controversial and policy statements must often be revised as new scientific data emerges. Those interested in the relationships, or inferences, between foods and non-nutrient food components and health should review and understand the criteria for causality as they make statements to the public, the media, and colleagues in the scientific community. The criteria have evolved over years of observation, experience, and research, and the following is a partial list of causal criteria that we will examine in this manuscript [1,4,5].

- Consistency: Replication of the findings across different studies.
- Strength of association: The magnitude of the relative incidence or mortality ratios.
- Biological gradient: A dose–response relationship is observed.
- Temporality: The cause must precede the effect.
- Specificity: One cause and one effect.
- Biological plausibility, mechanisms and coherence: The extent to which the association supports or conflicts with what is generally known about the biology of the disease.
- Experimental evidence: Data from a randomized clinical trial.

It is important to recognize that the use of inferential methods to determine causation may result in differences of opinion among well-respected investigators or expert committees. The current methods of inference are subject to criticism, remain qualitative and subjective, but will continue to be improved in the future. It is of interest to look at the current data regarding tomato products, lycopene, and prostate cancer in reference to the above criteria.

CONSISTENCY/REPLICATION

Research results that are consistently similar among various study designs, by different investigators, and in different target populations are a critical indicator of causality. Recently, Giovannucci [6] reviewed the published human epidemiologic studies that examined relationships between tomato consumption, lycopene (either serum lycopene or estimated dietary lycopene consumption), and prostate cancer risk. Of the 10 case-control and prospective epidemiologic studies evaluated, 8 found a reduced risk of prostate cancer for men with greater consumption of tomato products, higher estimated lycopene intake, or greater concentrations of blood lycopene and 6 of these studies reached statistical significance [6]. The recent update of the Health Professional's Follow-Up Study (HPFS) of over 47 000 American men reinforced the earlier findings [7]. However, not every study has detected this relationship. A recent case-control study of men developing prostate cancer at a young age (<60), perhaps a genetically predisposed subgroup, failed to detect any relationship between prostate cancer risk and consumption of tomatoes [8,9]. It is difficult to dissect the potential benefit of lycopene from the potential benefit from tomatoes by epidemiologic studies since the vast majority of lycopene is derived from tomato products (a covariate) in the American diet. In general, it is our opinion that the majority of epidemiologic studies support a protective benefit of tomato products against prostate cancer, but additional studies by various investigators in different cohorts would be welcomed. Future research may more clearly define the benefits of tomato products among subgroups based on age, race, genetics, or environmental exposures.

STRENGTH OF ASSOCIATION

The assumption is that the stronger the association, the more likely it is to be causal, while a weak association (low relative risks) is less reliable and more likely to be influenced by bias or confounding factors. The odds ratio (OR) or relative risk (RR) are important statistical tools used to define the strength of association between exposures and outcomes. The strength of association is typically the greatest obstacle to demonstrating causal relationships for specific dietary variables and cancer risk. For many cancers, the association between an individual dietary factor and cancer risk is small in comparison with potent risk factors such as tobacco or asbestos exposure. Prostate cancer appears to have a particularly complex etiology with many additive and interactive factors, each with a modest relative risk, contributing to overall risk. It is also important for readers to consider the sample size. Studies that have a favorable OR or RR but are limited in the number of subjects are less likely to indicate a truly causal relationship. Additionally, studies with a small number of subjects may not have the statistical power to detect real but moderate differences in cancer risk that we often expect from dietary variables.

The data regarding tomato products and prostate cancer risk are fairly consistent in regard to the magnitude of the benefit reported. A prospective study published in 1989 collected diet and health information from 14 000 Seventh-Day Adventists. After six years of follow-up, they found a 40 % reduction in prostate cancer risk among men consuming tomato products five times per week compared with men consuming tomato-based foods fewer than one time per week [10]. The HPFS [11] examined over 47 000 men enrolled in 1986, and dietary intake was estimated using a 131-item food frequency questionnaire (FFQ) that was completed once during the initial six-year follow-up period during which 773 cases of prostate cancer were observed. Several tomato variables were associated with a reduced risk of prostate cancer: raw tomatoes (RR = 0.74 for zero servings vs. 2–4 servings/wk, 95 % CI = 0.58– 0.93, p for trend = 0.03), tomato sauce (RR = 0.66 for zero servings vs. 2–4 servings/wk, 95 % CI = 0.49–0.90, p for trend = 0.001), and pizza (RR = 0.85 for zero servings vs. 2–4 servings/wk, 95 % CI = 0.57–1.10, p for trend = 0.05) [11]. In men who had more advanced prostate cancer (defined as either stage C or D), consuming 10 servings of tomato products per week was significantly protective compared with consuming fewer than 1.5 servings per week (RR = 0.47, 95 % CI = 0.22–1.00, p for trend = 0.03). Subsequent data from the HPFS cohort with longer assessment were recently published by Giovannucci et al. [7] and included 2481 cases of prostate cancer. The results

were similar: the highest quintile of lycopene intake was associated with a 16 % reduction in prostate cancer risk (RR = 0.84, 95 % CI = 0.73–0.96, *p* for trend = 0.003) and tomato sauce (which contains highly bioavailable lycopene) intake of 2+ servings per week compared with <1 serving per month was associated with a 23 % reduction in prostate cancer risk (RR = 0.77, 95 % CI = 0.66–0.90, *p* for trend = <0.001). Case-control studies of more limited power are less consistent, and suggest between 0 and 36 % risk reduction when comparing a diet rich in tomato-based foods (or estimated lycopene intake) with a diet low in tomato-based foods [12–16]. In general, a trend toward lower risk of prostate cancer by 20–40 % is seen in larger and well-controlled studies for men with a greater intake of tomato products.

BIOLOGICAL GRADIENT/DOSE RESPONSE

A relationship between dose and response can be one important indicator of causality. Greater levels of exposure to a cancer-causing agent should result in an increasing gradient of risk. For example, measures of tobacco exposure, such as cigarettes per day, packs per day, pack years, correlate strongly with lung cancer risk. For agents purported to decrease cancer risk (e.g., tomato-based foods or lycopene), higher levels of exposure should result in a decreasing gradient of risk. There are very few human studies thus far published with the statistical power to address this relationship. For example, the recent results of the HPFS follow-up study suggest an inverse dose–response relationship between tomato sauce intake and prostate cancer incidence. The RR for men consuming tomato sauce <1 time per month was 1.0, 1–3 times per month, RR = 0.96, 1 time per week, RR = 0.80, and >2 times per week, RR = 0.77 (*p* for trend <0.001) [7]. Future studies, as well as the HPFS with additional prostate cancer cases developing over time, will hopefully provide stronger data regarding the biological gradient for lycopene or tomato products and prostate cancer risk.

TEMPORALITY

Prostate cancer is a disease that appears to develop over decades, since premalignant lesions are common in men in the third decade of life, while cancer is observed much later [17]. A major obstacle to dietary studies in humans is the difficulty to accurately quantitate past dietary patterns throughout the life cycle, including childhood and adolescence. The development of FFQs provides a tool for estimating food consumption habits over long periods of time in large samples. Unfortunately, the application of FFQs to case-control studies is compromised by recall bias and thus is not considered as definitive as prospective studies for the assessment of diet and cancer relationships [18]. Furthermore, the ability of an FFQ to measure dietary habits from more than 10 years ago is uncertain [18]. In prostate cancer, we hypothesize that dietary patterns during puberty and adolescence may contribute to risk. Unfortunately, large prospective studies over a lifetime are simply not feasible. Thus, the HPFS remains the most definitive study providing temporal data regarding tomato products and prostate cancer risk, although the ability to assess diet in youth, adolescence, and early adult years is limited.

SPECIFICITY

Hill defined specificity as “one cause, one effect”, however, the 1964 Surgeon General’s Report allows that for diseases with multiple etiologies, this criteria may not be appropriate and that a lack of specificity is not reason enough to reject causality. The etiology of prostate cancer is clearly a complex interaction between genes and environment [19]. Tomato products will prove not to be the only variable influencing risk, and future laboratory and human studies must try to dissect the multiple additive and interactive variables that may influence prostate carcinogenesis.

BIOLOGIC PLAUSIBILITY/MECHANISMS

Evidence from human, animal, and cell culture studies that provide a plausible biologic mechanism is important in establishing causality. Our laboratory has recently completed a large study of NMU-androgen-induced prostate carcinogenesis in rats showing that freeze-dried tomato powder as part of a nutritionally adequate diet will significantly reduce tumor risk in a similar range as observed in human studies [20]. We feel that the ability to reproduce the epidemiologic association in a very carefully controlled rodent study with a single variable provides very important supportive data for a protective relationship. Lycopene is most frequently cited as the phytochemical mechanistically responsible for the anticancer properties of tomato products. Several groups have documented the presence of lycopene in the human prostate, have shown that its concentration varies with tomato product intake, and that measures of oxidative stress may be reduced when tomato products are consumed [21–24]. The ability of lycopene to act as scavenger of free radicals is considered the most likely mechanism that could account for the hypothesized beneficial effects, however, other mechanisms are under consideration [25]. Some studies suggest an inverse relationship between dietary lycopene intake and insulin-like growth factor (IGF-1) levels [22,26]. Mucci and colleagues [26] collected serum and FFQ data from 112 men. They found consumption of cooked tomatoes was significantly inversely related to serum IGF-1 levels. For each one-serving increase in cooked tomatoes, there was a decrease in serum IGF-1 levels of –31.5 % (95 % CI = –49.1 % to –7.9 %, $p = 0.014$). This is a small study, but the data are provocative considering the critical role that IGF-1 may play in prostate cancer risk. Our group [27] is evaluating the ability of polyphenols from tomato products to inhibit the IGF-1 intracellular signaling cascade. It is important to consider the array of other phytochemicals in tomato products, including various carotenoids and the polyphenols, as we investigate possible mechanisms. Although the mechanistic data thus far generated is intriguing, no definitive mechanism has thus far been established.

EXPERIMENTAL EVIDENCE/RANDOMIZED CONTROLLED TRIALS

Randomized clinical trials (RCTs) are designed to test hypotheses under controlled conditions that minimize the influence of confounders and minimize bias. RCTs are the most rigorous method used to evaluate scientific hypotheses regarding health and disease outcomes in humans. Ideally, RCTs are double-blinded, however, this is often impossible with food-based nutrition studies. Temporality (described above) is a major concern with nutrition and cancer randomized trials. Because prostate cancer takes decades to develop, a prospective RCT that measures prostate cancer incidence as an outcome can be expensive and may require decades of time, and it is difficult to insure that both the controls and intervention groups comply with a dietary change for an extended period of time. In our opinion, it will not be feasible to test tomato products in an RCT with prostate cancer risk as an outcome. Certainly, tomato products can be evaluated in short-term studies to examine bioavailability of phytochemicals and mechanisms of action, but much more work in this area will be necessary.

In contrast, we feel that the further development of lycopene must move forward with RCTs. In contrast to food products, pure chemicals can be employed in double-blinded studies to evaluate various outcomes. In the study by Kucuk et al. [22], which randomized men scheduled for a prostatectomy to either a lycopene-enriched tomato extract or no supplement, there were several statistically significant findings. Seventy-three percent of the lycopene-fed group had no spread to the surgical margins, compared with 18 % of the nonsupplemented group ($p = 0.02$) [22]. Additionally, diffuse high-grade prostatic intraepithelial neoplasia was found in 67 % of the intervention group compared to 100 % of the nonsupplemented group ($p = 0.05$). Although not statistically significant, prostatic-specific antigen (PSA) in the supplemented group decreased over the three-week study period from 6.89 + 0.81 ng/ml to 5.64 + 0.87 ng/ml and increased in the control group from 6.74 + 0.88 ng/ml to 7.65 + 1.78 ng/ml (p for difference between groups = 0.25). We feel very strongly that lycopene must be rigorously evaluated in phase I, phase II, and phase III human clinical trials in order to assure safety and efficacy.

Furthermore, laboratory studies in animal models may also provide important information regarding the ability of lycopene to act as a chemopreventive or therapeutic agent. It is only through a series of studies by various investigators that we can obtain the data we need to provide public recommendations regarding pure lycopene. Until a definitive series of studies are available, it is prudent to refrain from the consumption of pure supplements and support the consumption of tomato-based food products.

SUMMARY

The hypothesis that tomato products or lycopene may prevent prostate cancer and perhaps slow the progression of established disease is one of the most important concepts under study in the area of diet, nutrition, and prostate cancer. At the present time, definitive conclusions and recommendations remain controversial. However, ongoing research will continue to provide data regarding these relationships. At the present time, it is reasonable to recommend to the public that a diet rich in fruit and vegetables may contribute to a lower risk of many cancers. It is very reasonable to include tomato products as part of a healthy dietary pattern. In contrast, it is premature to suggest that the proposed benefits of a diet rich in tomato products can be achieved with supplements containing lycopene.

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