Promises and Perils of Lycopene/Tomato Supplementation and Cancer Prevention

Tomatoes or Lycopene: a Role in Prostate Carcinogenesis?[1]

Steven K. Clinton[2]

Molecular Carcinogenesis and Chemoprevention Program, The Ohio State University Comprehensive Cancer Center, Columbus, OH 43210

EXPANDED ABSTRACT

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The conundrum that we face regarding the potential role of tomatoes or lycopene as an inhibitor of prostate carcinogenesis has its foundation in epidemiologic data. The 1995 report from the large prospective Health Professionals Follow-up Study revealed a substantially lower risk of prostate cancer in men having a higher consumption of tomato products (1). Over the subsequent decade a number of additional epidemiologic investigations of various types and statistical power in different populations have been reported (2–4). In general, large prospective studies suggested a protective relation for tomato products, whereas case-control studies have been unconvincing and the relevance of these observations has been debated (5). My interpretation of the literature favors a modest beneficial effect, perhaps more strongly for sporadic prostate cancer, with less benefit against the cancers that occur in younger men, presumably related to a stronger inherited predisposition. Should we be interested in a food that may reduce overall risk by as little as 30, 20, or even 10%? My opinion is decidedly in the affirmative. Prostate cancer is a major public health problem, as the most common noncutaneous malignancy in affluent nations. The cost to our health care system of screening, diagnosis, and therapy in addition to the personal suffering resulting from the disease and its interventions motivates our continued efforts to elucidate the complex array of risk factors and define preventive interventions. Indeed, if tomato products are found, through additional studies, to reduce risk by even as little as 10%, future combinations of tomato products with other effective dietary components and chemopreventive agents may together provide a safe and potent regimen for prostate cancer prevention. Although additional prospective cohort studies and future pooling projects may enhance statistical power and provide greater insight into these relations, the modest benefits of tomato products may not be conclusively defined through epidemiologic studies alone. The hypothesis that certain subgroups may benefit a great deal, perhaps based on genetic or lifestyle predisposition, or that everyone benefits a small amount is another area of research that will be critical to pursue. Regardless, the epidemiologic literature provides enough data to warrant additional research and strongly suggests that we pursue the testing of hypotheses regarding tomato products and their constituents in carefully controlled experimental models of carcinogenesis and human intervention trails.

This topic also highlights the often contentious debate between the purveyors of nutritional or food-based approaches to cancer prevention versus the reductionist chemopreventive approach strongly rooted in pharmacology (6). The initial observations that tomato products are associated with a lower risk of prostate cancer immediately stimulated many investigators, educated in the modern era with a pharmacologic and molecular-targeting philosophy, to consider which component in tomato products might be the "active ingredient." Lycopene, the predominant carotenoid in tomato products, responsible for the familiar red color, immediately became the primary suspect (4,7). At this time, the vast majority of research activity has focused on lycopene, whereas very little effort has targeted other carotenoids or phytochemicals found in tomatoes (8). Lycopene is a potent antioxidant in chemical reactions and thus readily interfaced with other preconceived hypotheses regarding a role for oxidative stress (another poorly understood hypothesis) in prostate carcinogenesis (4,7). Lycopene and a variety of its isomers are found in human prostate at concentrations thought to have the potential for biological activity (9). Epidemiologic studies have employed databases of food composition to provide estimates of lycopene intake, although debate continues regarding how best to estimate intake when lycopene content of specific food items varies substantially. Lycopene intake or blood concentrations have been examined with regard to prostate cancer risk, with several positive and null reports (10,11). Interestingly, blood

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[2] To whom correspondence should be addressed.
E-mail: Clinton-1@medctr.osu.edu.

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lycopene is only weakly correlated with estimated intake from food questionnaires; thus blood concentrations are not very precise surrogate markers for overall tomato product consumption and exposure to the many other bioactive phytochemicals that may be contained in these products. The vast majority of dietary lycopene is not absorbed by humans, and ongoing studies suggest that the proportion absorbed and distributed to tissue is influenced by age, food source, food processing, cooking, mastication, other dietary components in the meal, hormonal status, and perhaps pharmaceuticals as well (12,13). Thus, given a modest relative risk reduction for tomato products to reduce prostate cancer risk, as suggested by epidemiologic studies, it is reasonable to predict that the relation between blood lycopene and prostate cancer risk can only be detected in carefully executed epidemiologic studies with substantial statistical power. Thus, lycopene remains a critical component of tomato products that warrants evaluation in carcinogenesis studies, although other substances found in tomato products must also be considered. In parallel, it is essential that we continue with efforts to examine tomato-based foods, representing a large array of phytochemicals that may have benefits beyond any single component.

An expanding assortment of rat and mouse models of prostate cancer tumorigenesis and carcinogenesis mimicking many features of human disease is now available (14). Unfortunately, very few have been employed to provide insight into the tomato, lycopene, and prostate cancer hypothesis. For these studies to be informative, it is critical that carefully designed dietary interventions are employed with detailed reporting of the dosage and composition of the components utilized. In addition, investigators must design studies with awareness that absorption of specific phytochemicals, such as lycopene, by rats and mice is substantially less than by humans and higher concentrations may be required in the diet to provide blood and tissue concentrations similar to that of humans (15). Several studies have been published supporting an inhibition of prostate tumorigenesis by lycopene in transplantable model systems (16). Remarkably, few carcinogenesis studies have been reported. One publication showed little benefit of lycopene, but dietary concentrations were such that in vivo concentrations were probably suboptimal to address an anticancer effect (17). A second study, which evaluated a combination of vitamin E, selenium, and lycopene in the *Lady* transgenic model, reported a substantial inhibition of cancer risk for the combination (18). Unfortunately, the individual effects of each component cannot be ascertained from this report. Our recent study (19) using the NMU (*N*-methyl-*N*-nitrosourea) and androgen-induced model of prostate carcinogenesis, examined prostate carcinogenesis in rats fed an AIN93G-based control diet, lycopene beadlets (Hoffmann-La Roche) providing total lycopene at 161 mg/kg of diet, or a freeze-dried whole tomato powder (Armour Foods) at 10% of the diet providing lycopene at 13 mg/kg of diet. We observed no anticancer effect of lycopene compared to the control group. However, risk of death with prostate cancer was lower for rats fed the tomato powder diet than for rats fed the control diet (hazard ratio of 0.74, $P < 0.009$). Interestingly, the lycopene-fed rats demonstrated higher blood lycopene content but did not show a reduced risk of prostate cancer. Thus, our rat carcinogenesis study supports the concept that tomato products may contain multiple other components that contribute to anticancer activity. It is imperative that lycopene and tomato products be evaluated, preferably with a range of dosages, in multiple models that mimic characteristics of human prostate carcinogenesis. These studies will provide additional insight into efficacy, safety, and biomarkers relevant to the design of future intervention studies in humans. Of critical relevance to humans with prostate cancer, animal models provide an efficient mechanism to examine tomato products or lycopene in combination with other chemopreventive agents or to consider interactions with therapeutic modalities such as androgen deprivation, radiation therapy, and commonly employed chemotherapeutic agents including taxanes, anthracyclines, platinum, and newer molecularly targeted agents.

CONCLUSIONS

At this time, it is premature to make specific public health recommendations or government-sanctioned health claims for tomato products or lycopene in regard to prevention or treatment of prostate cancer. It is reasonable to suggest that the consumption of tomato products can help an individual achieve the current goal of increased fruit and vegetable consumption by all Americans. Ultimately, only through clinical trials will we establish the role of tomatoes or lycopene in prostate cancer prevention or as an adjunct to therapy. A number of clinical studies are now underway, with several recently published (20,21). Although limited in statistical power and scope, several studies suggest that consumption of tomato products increases blood and prostate lycopene while favorably influencing markers of oxidative stress, prostate-specific antigen, or tissue biomarkers (20–22). Future studies, with careful attention to statistical power and experimental design and with appropriate controls, are clearly needed. These critical studies will focus on various phases in the natural history of human prostate cancer, including prediagnosis and prevention, hormone-sensitive disease, and hormone-resistant disease. Human studies will also provide critical data regarding safety and efficacy of phytochemicals at concentrations that may exceed those typically found in the diet. It is vital that we do not make assumptions about the safety of phytochemicals when we are undertaking clinical trials in aged men who suffer from a variety of comorbidities, are often consuming a variety of medications, and may be undergoing surgical or radiation therapy for prostate cancer. Safety must be proven with the same diligence as is devoted to efficacy.

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