Tomatoes or Lycopene Versus Prostate Cancer: Is Evolution Anti-Reductionist?

Peter H. Gann, Frederick Khachik

Occasionally, but not often, positive things happen in the field of cancer prevention science to popular, good-tasting foods. Cruciferous vegetables have been the subject of intense study, but these foods might be—to modify the expression—an easy pill but a hard food for the public to swallow. By contrast, tomatoes (scientifically classified as a fruit) have overcome their earlier reputation as an inedible and possibly toxic food to become one of the most heavily consumed fruits or vegetables in the Western diet—mostly in the form of pizza, salsa, chili, pasta sauce, and ketchup. Americans consume an average of 91 pounds of tomatoes per capita per year, second only to potatoes among all fruits and vegetables.

This issue of the Journal brings good news to tomato eaters. Boileau et al. (1) report, in a well-controlled study using the N-methyl-N-nitrosourea (NMU)–androgen rat carcinogenesis model, that a diet containing whole tomato powder inhibited the development of prostate cancer compared with a control diet, whereas a diet containing a pure synthetic lycopene supplement did not. In the tomato powder group, the risk of developing lethal prostate cancer was reduced by a statistically significant 26% compared with that in control rats; by contrast, the group receiving lycopene experienced only a 9% (and not statistically significant) risk reduction compared with controls. Using a factorial design, the investigators also measured the effect of a 20% dietary calorie restriction on the risk of dying with prostate cancer. The authors found that this restriction on energy intake produced a 32% reduction in prostate cancer mortality that was independent of (i.e., additive to) the effect of tomato powder.

This new study is important and provocative on several levels. Perhaps most important, it weighs heavily in the debate about whether cancer prevention is best achieved via whole foods versus via single compounds. Readers are no doubt familiar with the β-carotene story: After years of research indicating a possible benefit of supplemental β-carotene against lung cancer, two phase 3 randomized trials found that a β-carotene supplement was not only ineffective but actually appeared to increase lung cancer risk, primarily among smokers (2). This is the best known but not the only adverse experience in humans taking carotenoid supplements. For example, canthaxanthin, another carotenoid that is still marketed as an artificial tanning agent, is known to cause a reversible crystalline retinopathy in people who take high doses (3). A possible reason for the misleading observational results on β-carotene is that, given the sources of β-carotene in the diet, people who eat a lot of it (and therefore who also have higher concentrations in their serum) tend to have healthier diets and lifestyles. Lycopene/tomato research is not plagued by this difficulty—in fact, heavy lycopene consumers in the United States have essentially the same patterns of exercise, body weight, and smoking as lighter consumers (4). Given this background, it is important to note that most observational and indeed human experimental evidence to date concerning the possible benefit of lycopene versus prostate cancer is actually based on consumption of lycopene-rich foods such as tomatoes rather than lycopene itself, which has not been used as a supplement long enough or widely enough to facilitate epidemiologic research. In studies relating serum or plasma concentrations to risk, lycopene concentrations might only serve as a marker for consumption of the relevant foods (5).

The ultimate biologic activity of a given food or nutrient depends on a large number of variables, including food processing and preparation method, gastrointestinal tract physiology, interactions between compounds in the food, and interactions between foods eaten together at the same meal. The biologic effect of a given food might even be influenced by how rapidly we eat it, as is seen in the literature on glycemic load. It has already been established that heat, mechanical processing, and ingestion together with oil or fat alters the bioavailability of lycopene and similar compounds by releasing them from intracellular compartments and promoting intestinal absorption (6). In addition to lycopene, known carotenoids in tomatoes and tomato-based products include β-carotene, γ-carotene, ζ-carotene, phytofluene, and phytoene, all of which are among the 10 major carotenoids that have been found to accumulate in human prostate tissue (7). The article by Boileau et al. does not present detailed qualitative and quantitative analyses of these carotenoids in tomato powder, plasma, and prostate tissues of the treated rats—such analyses, in view of the results of the experiment, would be useful in clarifying the possible role of other tomato carotenoids that may exert their biologic effects in concert with lycopene. As the authors mention, there are also numerous non–carotenoid compounds in tomatoes that have potentially relevant activity, and certainly a large number of unknown phytochemicals as well.

Carotenoids generally occur in the plant for a purpose, for example, to protect seeds in fruit from photodegradation and oxidative damage. From an evolutionary perspective, it makes sense that plants would develop sets of interacting compounds to...
accomplish these functions rather than relying on single compounds. This strategy provides redundancy and allows for a more subtle play of natural selection, because minor modifications in an enzyme could affect a web of active metabolites or interacting compounds. Such complexity is not unreasonable when you consider, to paraphrase the author Michael Pollan in his recent book *The Botany of Desire* (8), that while humans were learning how to walk upright, plants were continuing the process—hundreds of millions of years old—of developing intricate chemical methods to compensate for their relative immobility. Even biochemical systems that appear to have evolved for a simple straightforward effect, such as toxins, are in fact quite complex. Snakes, for example, which are ancient in comparison to most animals but are newly arrived by plant standards, have evolved venoms that are strikingly complex. We have barely begun to scratch the surface of understanding how the compounds within tomatoes interact within biologic systems. Studies such as that by Pastori et al. (9) on the interaction of lycopene and α-tocopherol in prostate cell cultures stand as testimony to how limited this knowledge is so far. Given the potential complexity of the relevant effects in humans, untangling these interactions in the laboratory—essentially subjecting them to reductionist analysis—could be a long and tedious process.

The timely study by Boileau et al. is well-designed and conducted, especially considering the challenges posed by animal models for prostate cancer and the general demands of dietary intervention studies. Nevertheless, given the importance of the results, alternative explanations, even relatively unlikely ones, should be considered. The study was designed to deliver considerably more lycopene to the pure lycopene group than to the tomato powder group, but perhaps coincidentally, the plasma lycopene concentrations came out nearly equal. Although the plasma compartment might have been saturated for lycopene, we do not know the relative concentrations in tissue, and it is conceivable that the biologically effective dose in tissue was too high to inhibit tumor growth in the lycopene group. This possibility should be explored as an alternative explanation for the lower efficacy of lycopene than of whole tomato powder, because nonmonotonic and even U-shaped dose–response curves have been reported for protection against cell damage by both lycopene and β-carotene (10). It also appears that a substantial amount of lycopene in both the lycopene and tomato powder diets was lost after exposure to the light, atmosphere, and temperature of the rat cages, which is somewhat surprising for the lycopene diet, because the lycopene was present as beadlets, which are normally stable. Lycopene breakdown products consist of a number of in-chain cleavage products, such as apolycopene, apolycoprenals, and apolycoprenoic acids. In addition, it has been shown that acycloretinal, one of the oxidation products of lycopene, can be converted to acycloretinoic acid in the presence of pig liver homogenate (11). Although the biologic properties of lycopene degradation products are not known at present, different rates or patterns of degradation between diets would result in the formation of a number of breakdown products that could be responsible for the enhanced efficacy of tomato powder compared with lycopene. This situation can become even more complex because other tomato carotenoids may be similarly subjected to degradation to smaller molecules with unknown biologic properties. Carefully controlled stability studies throughout preparation and storage of the diet would be needed to eliminate these uncertainties.

An unusual and methodologically significant aspect of this study is the use of morbidity (presumably due to prostate cancer) as an endpoint rather than scheduled sacrifice of the animals at fixed intervals. This design permitted a survival (time–event) analysis that closely mimics a human trial that could have been conducted in the pre–prostate-specific antigen era. The main advantage of this design feature is that it evaluates the effect of treatment on prostate cancer that is undoubtedly biologically important, albeit to a rat. Recent problems with interpretation of the Prostate Cancer Prevention Trial of finasteride foretell how difficult it will be in human trials to identify clinically significant effects on prostate cancer incidence in the face of prostate-specific antigen surveillance and biopsy at fixed timepoints (12). The main risk of this design aspect, however, is that it can introduce bias if the morbidity that triggers vivisection of the animals is not always due to prostate cancer, and if the groups receiving different treatments differ in their likelihood of getting sick due to causes other than prostate cancer. Information on the attribution of morbidity leading to vivisection, and on the blinding of technicians responsible for this decision, should be discussed as the results of the study are examined further.

Although this one study—like one molecule—is not likely to be definitive, it will, as all important studies do, open and clarify avenues for research. The mechanisms of action of tomato powder in the NMU model can be explored fruitfully (for example, effects on the androgen and insulin-like growth factor systems), as can the efficacy of this agent in other types of rodent models, including xenografts and transgenics. Investigators designing phase 2 trials in humans can also take note of these findings and begin testing foods and food derivatives in addition to pure lycopene. Successful completion of these studies could mean that a phase 3 trial is not far off. It is important to remember the somewhat obvious point that whole food or dietary trials in humans cannot be placebo controlled. In dealing with the relationship of diet to cancer causation or prevention, we would do well to emulate the “wisdom” of the evolutionary process and use only as much reductionism as is necessary to understand where we are and where we are going.

**REFERENCES**


7. Pauata I, Khachik F, Brown ED, Beecher GR, Kramer TR, Chittams J, et al. Chronic ingestion of lycopene-rich tomato juice or lycopene supple-


