Is Lycopene an Effective Agent for Preventing Prostate Cancer?

Michael B. Sporn and Karen T. Liby

Abstract

The role of lycopene, an open-chain carotenoid found in tomatoes and devoid of retinoid activity, as an anticarcinogenic, chemopreventive agent, especially for use in prostate cancer, is still under active investigation. In this issue, Qui and colleagues show that lycopene induces responses in human prostate epithelial cells that are antiproliferative, antioxidative, and anti-inflammatory, as well as downregulating targets in the androgen receptor signaling pathway. In this perspective, we review aspects of the molecular and cellular biology of lycopene that support its use for prevention of prostate cancer. Whether lycopene itself or its metabolites induce most of its benefits is still uncertain. At present, meta-analysis of clinical studies of lycopene for prevention of prostate cancer in men does not yet support the definitive clinical use of this carotenoid in a preventive setting. Cancer Prev Res; 1–3. ©2013 AACR.
epithelial cells, which they have established in culture from surgical specimens, as the reader cells rather than less relevant malignant prostate cells such as LNCaP or PC-3. However, effects of lycopene on the various cells of the microenvironment, which can be so important for chemoprevention (8, 9) of cancer, were not evaluated in the present study. Overall, the present data suggest that lycopene is active in suppressing cancer initiation, promotion, and/or progression rather than at later stages of carcinogenesis; similar conclusions have previously been published.

There is no question that lycopene is indeed a multifunctional compound (1); in no way does it fit the current fashion for single-targeted drug therapy for either prevention or treatment of cancer. Not only is lycopene highly reactive toward oxygen and free radicals, it has a range of other mechanistic actions that are highly relevant to suppression of carcinogenesis. These include induction of apoptosis, anti proliferative, and antimetastatic activity, as well as the induction of cytoprotective “phase II” enzymes that inhibit the carcinogenic effects of many xenobiotics (1, 10). This latter effect is mediated by enhancement of the activity of the transcription factor, Nrf2, which results in increased transcription of cytoprotective genes regulated by the antioxidant response element on DNA. Lycopene was most potent of a series of carotenoid molecules tested in this regard (10).

Moreover, it has been amply shown that lycopene itself is converted to a large number of metabolites. These conversions include isomerization of the trans-double bond system of the 40-carbon molecule, as well as cleavage and hydroxylation of many of the double bonds (11, 12). It has been suggested that, “there is limited experimental support for the (direct) antioxidant hypothesis as a major mechanism of lycopene’s in vivo action” and that instead, “metabolic products of lycopene, the “lycopenoids”, may be more active than the parent molecule” (12). Furthermore, in this analysis, the desirable effects of the lycopenoids are suggested to be the result of alterations in gene expression.

The ultimate use of this entire approach to prostate cancer rests on its effectiveness in vivo, particularly in human subjects. Attempts to show preclinical efficacy in animal models of chemoprevention of prostate cancer have thus far not been impressive. Although statistically significant, when chemopreventive results have been reported in transgenic (TRAMP) and chemically induced (nitrosomethylurea plus testosterone) mouse (13) and rat (14) models, the effects were not particularly striking. Indeed, in the latter model, tomato powder was more effective than lycopene itself.

Final clinical proof of efficacy has been difficult to obtain. Oral administration of lycopene extracts to men with prostate cancer or benign prostatic hyperplasia caused major increases in lycopene levels in both prostate biopsies and plasma. However, in the same patients, no beneficial effects on biomarkers of oxidative stress and lipid peroxidation, such as 8-oxo-deoxyguanosine or malondialdehyde, were observed in either prostate tissue or plasma (15).

Similarly, 2 major recent retrospective studies (2, 3), which have surveyed many clinical trials for the potential benefits of lycopene supplements for prevention and treatment of prostate cancer, have failed to support any true optimism that lycopene itself will be an effective clinical chemoprevention drug. Fortunately, however, there is no evidence that lycopene can increase human cancer incidence, as has sadly happened with β-carotene in clinical trials (16–18). Although lycopene did decrease plasma PSA levels in some trials, the ultimate conclusion of the latest systematic review is that, “given the limited number of randomized clinical trials published, and the varying quality of existing studies, it is not possible to support, or refute, the use of lycopene for prevention or treatment of benign prostatic hypertrophy or prostate cancer” (3).

Perhaps, like many other natural products that can be shown to prevent cancer in experimental animals, lycopene is simply not potent enough to be a clinically useful drug. Concentrations in excess of 1 μmol/L are necessary to achieve biologically meaningful responses. Perhaps what is needed is to build upon what has already been shown, namely that lycopene does indeed have some chemopreventive activity but then to chemically modify this natural product scaffold to make more potent derivatives (19, 20). Such new semisynthetic derivatives hopefully will then be able to deliver the preventive results that are needed so urgently.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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