

Meeting Report

International Symposium on the Role of Lycopene and Tomato Products in Disease Prevention

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An international symposium in a new area of chemoprevention was held on March 3, 1997, in the New York City facilities of the American Health Foundation. It was sponsored by the American Health Foundation and the Tomato Research Council of New York. The program was organized by Dr. John H. Weisburger, Senior Member of the American Health Foundation, who chaired the sessions.

The interest in lycopene, the red coloring agent of the tomato, which has demonstrated antioxidant properties, stems largely from epidemiological observations such as those reported by Dr. Edward Giovannucci and colleagues at the Department of Nutrition of the Harvard School of Public Health. They indicate an association of tomato consumption with a significant (up to 34%) reduction of the risk of prostate cancer among 48,000 health professionals. Moreover, Dr. Carlo La Vecchia, Head Epidemiologist at the Mario Negri Institute for Pharmacological Research in Milan, reported that in Italy, where tomatoes are a highly prevalent component of the Mediterranean diet, there is a consistent protective pattern from tomato use for digestive tract cancers. A study conducted by Dr. La Vecchia and his associates on the basis of data from 1983-1992 included evaluations of histologically confirmed cancer cases, of which 317 were of the oral cavity and pharynx, 85 were of the esophagus, 723 were of the stomach, 955 were of the colon, and 626 were of the rectum. These were compared against a total of 2879 controls. Adjusted for age, sex, study center, education, smoking, alcohol consumption, and total caloric intake, the data showed for the highest tomato consumption quartile ORs of 0.65 (95% CI, 0.04-1.0) for oral cavity, pharynx, and esophagus; 0.43 (95% CI, 0.3-0.6) for stomach; 0.39 (95% CI, 0.3-0.5) for colon; and 0.42 (95% CI, 0.3-0.6) for rectal cancer. In a follow-up study based on 1953 cases and 4154 controls that was conducted between 1992 and 1996 with a more detailed food questionnaire, the protective effect of tomato consumption for colorectal cancer was confirmed, even when it was adjusted for confounders such as body mass index, caloric intake, and physical activity, giving ORs for the highest consumption quintile of 0.79 (95% CI, 0.6-0.9) for colon cancer and 0.71 (95% CI, 0.5-0.9) for rectal cancer. Whereas the studies in the United States had indicated that the highest protective effect is

achieved with processed tomatoes, primarily tomato sauces and pizza, the data in Italy measured total, mainly cooked, tomato consumption. This points to the importance of studies on uptake and distribution of the active protective principle, which were addressed in the course of the symposium.

There appears to be agreement that the observed protective effect is based largely, though perhaps not solely, on an antioxidant mechanism; thus, the effect of tomato consumption is not unlike effects observed with high intake of fruits and vegetables in general. What makes the tomato different, and perhaps unique, is its high content of lycopene, the carotenoid that imparts the bright red color, explained Dr. Norman Krinsky, Professor of Biochemistry at Tufts University School of Medicine (Boston, MA), in his overview on lycopene, carotenoids, and disease prevention. He stated that the high hopes placed in β -carotene as a naturally occurring chemopreventive agent in human intervention studies had evaporated when, even after a 12-year period of supplementation, this carotenoid had failed to yield benefits among persons at high risk for lung cancer, namely heavy cigarette smokers and asbestos workers. These studies had raised the question of whether β -carotene was the right carotenoid to study, or whether combinations of carotenoids or of carotenoids and other phytochemicals would have to be applied to achieve the protective effects seen in epidemiological surveys of populations with high intake of fruits and vegetables that are rich in such nutrients.

Meanwhile, we have learned from experiments with cells in culture, from *in vivo* bioassays, and from studies on the localization of specific carotenoids in certain tissues that other carotenoids may indeed hold greater promise than β -carotene. Lycopene may play a role in the suppression of prostate cancer development, zeaxanthine and lutein may be involved in age-related macular degeneration, and there is evidence that α -carotene kills tumor cells in culture. Thus, researchers are challenged to focus attention on the carotenoid family as a whole, as well as on its individual components.

Moreover, it will be important to study mechanisms of interaction or "cooperation" of plant phytochemicals and pigments, such as the carotenoids, as nutrients that inhibit cancer. More than 100 phytochemicals can be found in fruits, legumes, and vegetables. More than 600 different carotenoids are known as naturally occurring substances, of which the body uses perhaps 50. Because the human body does not produce carotenoids yet needs them as essential micronutrients, eating a wide variety of vegetables and fruits is necessary to ensure adequate intake.

United States 1995 production was 1.1 million tons of fresh and 11.3 million tons of processed tomatoes, according to Dr. Gary R. Beecher, Research Chemist at the Food Composition Laboratory of the United States Department of Agriculture Nutrition Research Center (Beltsville, MD). The tomato and its various products richly supply vitamin C, potassium,

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² The abbreviations used are: CI, confidence interval; OR, odds ratio.

folacin, and phytonutrients; lycopene is the most prominent among a spectrum of carotenoids. In view of its rich content in provitamin A compounds, γ -carotene, and β -carotene, the tomato is certainly one of the primary carriers of antioxidants.

What happens to all of these micronutrients, and especially to lycopene, in the course of food processing? This question was addressed by Dr. Steven Schwartz, Professor of Food Science and Technology at Ohio State University. In model experiments on the stability of lycopene, both thermal and oxidative decomposition was demonstrated *in vitro*, whereby lycopene was found to be even more susceptible to oxidative degradation than β -carotene; however, during food processing of tomatoes and tomato products, lycopene appeared to be relatively stable, and only low levels of *cis*-lycopene were formed during typical thermal treatment. Interestingly, it is the *cis* form of lycopene that is found in high quantities within physiological fluids, such as serum, or in body tissues, such as the prostate. Whether these isomers appear in this form as a result of conversion of dietary products or due to other mechanisms needs to be examined.

How then does the human body absorb and transport carotenoids? Studies by Dr. John W. Erdman, Jr., Director of the Division of Nutritional Sciences at the University of Illinois (Urbana, IL) shed some light on this question. Lycopene and other carotenes are lipophilic and thus require appropriate digestion and incorporation into lipid micelles within the gastrointestinal tract to be absorbed. Lipid micelles will be formed only when the digest contains sufficient fat, causing the release of bile acids and salts from the gall bladder. Dietary fat also allows for the transfer of lycopene from intestinal mucosal cells into chylomicrons, which are then carried via the lymph system into the bloodstream and to the various body tissues. Dr. Erdman said that the presence of protein-carotene complexes in food; high quantities of soluble dietary fibers, such as pectins; or cholesterol-binding resins (*i.e.*, fat substitutes), as well as intestinal diseases, allergies, or parasites can interfere with the absorption of lycopene.

In rats, lycopene given at a range of 50–1200 ppm in a 4% lipid suspension derived from tomatoes was readily absorbed and stored in the liver in a dose-related manner, observed Dr. Leonard A. Cohen, Head of the Section of Nutritional Endocrinology at the American Health Foundation. Tissue distribution studies led to the finding that lycopene levels in rat serum were not linearly related to dietary intake and that lycopene concentration in the liver was 2 orders of magnitude lower than that in serum or tissues. Forty to 500 ng of lycopene were found in the lungs, prostate, and mammary tissues of the rats. Although rats are less favored than ferrets for comparison with human uptake and tissue distribution of carotenes, the fact that uptake and tissue distribution do occur allows chemoprevention studies in well-established model assays to further elucidate the efficacy of lycopene as a cancer-protective micronutrient.

A review of studies on the bioavailability of lycopene to humans and serum response to it was presented by Dr. Elizabeth J. Johnson, together with Dr. Robert M. Russell; both are researchers at the Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University. They showed that lycopene, as a major carotenoid in western diets, is also a predominant carotenoid in the serum of individuals in the United States, accounting for 40% of the total blood carotenoids in Americans, whereas less than 10% is found in Asians. In comparison to other carotenoids, lycopene concentrations are especially high in the testis,

adrenal gland, and prostate, where they make up 60–80% of the total carotenoids. Lycopene predominates also in the liver, lung, and kidney. Serum lycopene levels are not higher in women than in men. Smokers have decreased serum levels of β -carotene, lutein, zeaxanthin, and cryptoxanthin when compared to nonsmokers; however, this difference does not exist for lycopene (perhaps due to nicotine). Heavy alcohol drinking is associated with lower serum levels of carotenoids; this is confirmed by serum analyses showing that moderate drinkers of alcohol have greater lycopene concentration in serum than heavy drinkers, and abstinence from alcohol leads to a significant increase of serum lycopene. Studies on possible interaction of carotenoids that would affect bioavailability and absorption of lycopene are ambiguous thus far, ranging from the observation that a decrease in serum lycopene occurs when high doses of β -carotene are present, to reports that no interaction took place and, on the other end of the spectrum, that serum lycopene increased after chronic high dose intake of β -carotene. In view of the importance of emerging data on the role of lycopene as a protective factor against development of cancer at several sites, studies on the metabolism and biological function of lycopene are urgently needed.

Characterizing lycopene as a carotenoid present in human blood at levels of ~ 0.5 mol/liter plasma, with tissue levels varying from 1 nmol/g wet weight in adipose tissue to up to 20 nmol/g wet weight in testes and adrenals, Dr. Helmut Sies, Professor of Physiological Chemistry at the Heinrich Heine University (Düsseldorf, Germany), provided a closer look at the biological functions of this interesting tomato pigment. Among the remarkable activities of lycopene are its singlet oxygen quenching and peroxy radical scavenging (lipid peroxidation inhibiting) properties, its induction of cell-to-cell communication, and a role in the control of proliferation of tumor cells. Unlike some of the carotenoids that accompany it, lycopene has no provitamin A activity. Lycopene is capable of inducing gap junctional communication, but its effects are less pronounced than those of β -carotene and canthaxanthin. In line with observations by other researchers, Dr. Sies and his collaborators found that serum levels were elevated after intake only when tomato juice was given after being heated in the presence of some vegetable oil. Ingestion of tomato paste elevated lycopene in chylomicrons 2.5-fold above levels induced upon consumption of fresh tomatoes. Thus, cooked tomatoes with olive oil, as traditionally used in Italy and discussed by Dr. La Vecchia, seem to yield optimal tissue concentrations of lycopene.

Lycopene holds active research interest because of its promise as a protective, if not an agent, against prostate cancer. Dr. Steven K. Clinton, Instructor in Medicine at Harvard Medical School and Clinical Associate at the Dana-Farber Cancer Institute, therefore delineated the complex pathogenesis of prostate cancer and described why much hope is placed in the mediating effects of dietary components, including substances in tomatoes that may be regarded as modulators of carcinogenesis. Dr. Clinton characterized the concentration of lycopene, other carotenoids, and retinol in prostate tissues from American men. Lycopene and all-*trans*- β -carotene were the predominant carotenoids. They also evaluated tomato-based food products, serum, and prostate tissue for the presence of lycopene isomers, finding that all-*trans*-lycopene constitute 79–91% and *cis*-lycopene isomers constitute 9–21% of total lycopene in tomatoes, tomato paste, and tomato soup. In sharp contrast to this, all-*trans*-

lycopene constitute only 12–21% and *cis*-isomers constitute 79–88% of total lycopenes in prostate tissues, whereas serum concentrations reflected a composition of 27–42% all-*trans* and 58–73% *cis*-isomers. Cell culture studies and rodent model assays for prostate cancer are under way to delineate mechanisms and explain the significance of the isomeric conversions.

Dr. Clinton cautioned that it is too early to assume that benefits seemingly associated with consumption of tomato products can be achieved by merely administering a lycopene

supplement, and he agreed with Dr. Weisburger and the other participants in this symposium that a diet rich in fruits and vegetables, including tomatoes, is an appropriate recommendation for the public, on the basis of current knowledge. However, the evidence reviewed and presented at this international meeting also gives new impetus for research and much hope that the data emerging in the near future will shed considerable light on mechanisms of cancer induction and prevention and lead to appropriate changes in nutritional and lifestyle traditions in the world.