Lycopene and Tomato Products in Health Promotion[1]

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International research through epidemiological techniques has provided information on risk factors and preventive approaches in chronic disease. Causation complementing this base of knowledge with laboratory research on associated markers for each disease has outlined the possible mechanisms whereby risk factors and preventive conditions operate. Furthermore, laboratory research in animal models and cell cultures has expanded the appropriate elements associated with each condition. Individuals in the Mediterranean area present with a lower risk of several important chronic diseases, including coronary heart disease and a number of types of cancer associated with nutritional traditions, such as breast, colon, and prostate cancer. Vegetables and fruits in general and cooked tomatoes, together with olive oil, appear to be the nutritional traditions that account for this lower risk. These results lead to public health recommendations to consume more vegetables and, especially, cooked tomatoes with olive oil. Exp Biol Med 227:924–927, 2002

Geographic pathology has provided important and relevant information on elements associated with chronic disease causation and factors that may relate to disease prevention (1, 2). Thus, comparison of the incidence of heart disease and many types of cancer between the United States and those Japanese consuming a traditional, non-Western diet, Japanese diet has led to the conclusion that the intake of a high-fat diet, including saturated fats from meats and dairy products as well as mixed oils, represent a high-risk situation in the United States. In contrast, in traditional Japan the dietary traditions were a relative low dietary fat intake, including the omega-3 polyunsaturated oils from fish. These epidemiologic studies were complemented by laboratory research demonstrating that saturated fats were associated with heart disease and the omega-6 polyunsaturated oils at 40% of calories with specific types of cancer such as in the breast, colon, prostate, and pancreas. On the other hand, the omega-3 polyunsaturated oils were protective in heart disease and the nutritionally linked cancers mentioned previously (3, 4).

Another interesting comparison was between people in Finland, particularly rural Finland and United States, or Denmark (5, 6). People in Finland displayed a high rate of heart attack, which was attributed to the appreciable consumption of milk, an important food for children, but which in adults increases the risk of coronary heart disease mainly through its content of lactose, the atherogenic principle. Yet, the incidence of breast and colon cancer in Finland is low, almost at the levels observed in Japan. The explanation was the traditional consumption of appreciable levels of Finnish rye bread, which led to the excretion of a large stool, about 250 g a day, compared with 80 g per day in the United States or in Denmark. There are gradations in this context. In Northern Sweden, the risk of colon and breast cancer is somewhat higher than in Finland, but in Southern Sweden or in Denmark, it is similar to that found in the United States. The underlying mechanism and marker relates to different amounts of whole grain and rye bread and the consequent stool size, diluting bile acids, promoters for colon cancer, or modifying the enterohepatic cycling of estrogen associated with risk of breast cancer (7).

A third set of data stem from epidemiological studies in the Mediterranean region, particular Southern Italy and Greece (8–13). People in this region display a low to moderate risk of heart disease and of the nutritionally linked cancers mentioned above. One underlying mechanism in this instance relates to the traditional use of a monounsaturated oil, olive oil. Studies in humans and in laboratory animals show that this type of oil presents a relatively low risk of coronary heart disease and of the nutritionally linked cancers. These findings were made in laboratory animals that permitted the exploration of the mechanisms and markers of risk. Actually, olive oil is marketed in different versions, extra virgin, from cold pressed olives that also contain some beneficial antioxidants, to less-expensive olive oils that are produced through other means. In addition, people in the Mediterranean region do not consume much milk as such but do enjoy dairy products such as cheese and yogurt without lactose, accounting, in part, for the lower disease risk (7). Of greatest importance is the customary

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intake of vegetables with most meals so that the total intake in the Mediterranean countries represents the 5 to 10 vegetables and fruits considered as an optimal goal in the United States. One important component of the Mediterranean diet is the regular intake of cooked tomatoes and cooked tomato products as part of the vegetable regimen that is often used with starchy foods, such as pasta. Table I summarizes these aspects of geographic pathology.

Historically, the tomato *Lycopersicon esculentum* was a plant growing wild in northwestern South America, Central America, and Mexico. It was introduced, apparently, in Spain in the 16th century, and thence in Italy and the Eastern Mediterranean area. Interestingly, references to tomatoes in the United States dated back to the 18th century, and the plant came from Europe, not its original home in Latin America (14).

Vegetables and fruits are good sources of vitamins and minerals. However, the major components include other antioxidants. This is important because essential oxygen inhaled can be converted by cellular enzyme systems to reactive oxygen species (ROS) such as hydroxy radicals, peroxides, and other reactive oxygen components (16, 17). These are hazardous because they are reactants that convert low-density lipoprotein (LDL)-cholesterol to the reactive oxidized form, the actual risk factor for heart disease. ROS also can modify essential proteins and enzymes, but most importantly, they are powerful intermediates to alter DNA in genes, leading to mutational events that represent the initiation processes for virtually all types of cancer. It is important to stress, therefore, that the formation and presence of ROS need to be eliminated or minimized. A major method to achieve this goal is to ensure nutritional habits with antioxidants present in fruits and vegetables, where vegetables seem to have a slightly larger relevance (8). Incidentally, products such as soy-derived foods and green or black tea also are excellent sources of defensive antioxidants that play a protective role in Asia, particularly in Japan, Korea, and parts of China (2, 4, 7). However, these foods are not usually part of the Mediterranean dietary tradition.

The traditional intake of tomatoes in the Mediterranean region is an especially relevant aspect of the locally prevailing nutritional tradition. Tomatoes are rich in carotenoids, especially lycopene. This product is a long chain polyunsaturated aliphatic compound, in part similar to carotene. It exists in a number of stereoisomeric forms. Tomatoes contain mostly the *trans* forms, but light irradiation or cooking converts part of the *trans* form to the *cis* configuration. It seems this could also occur *in vivo*. All forms of lycopene are fairly water insoluble. In the tomato itself, lycopene is attached to membranes and is not released very easily. During the cooking of tomatoes, this bond of lycopene to membranes is weakened, and for that reason cooked tomatoes make available larger amounts of lycopene than fresh tomatoes. Incidentally, this is also true for carotene in vegetables, such as carrots. In addition, lycopene, because of its chemical structure, is a fairly nonpolar compound that dissolves much better in oils, such as olive oil. This is why the Mediterranean nutritional tradition, consuming cooked tomatoes as part of a diet containing olive oil, provides not only for optimal release of lycopene ingested as part of the total diet, but also is efficiently absorbed together with the olive oil, and thus, can reach tissues and cells.

Worldwide, prostate cancer shows the third highest in-

Table I. Geography Pathology as Means to Explore High and Low Risk Areas of Chronic Diseases

Area	Enhancing factors	Protective factors
United States	High CHD,[a] cooked meat, milk, obesity, high postmenopausal breast, distal colon, rectum, prostate, pancreas, browned meats, total fats, high fat and salt snack foods, low vegetables and fruits, lack of exercise	Low stomach cancer, low salt, low *Helicobacter pylori*
Finland	CHD, milk	Breast and colon cancer, High-bran fiber rye bread
France	Smoking and alcohol, high esophagus cancer (regional)	CHD, low adult milk intake, vegetables, red wine, smaller food portions
Mediterranean Area		CHD, nutrition-linked cancers, especially prostate, little browned meat, high fish, vegetables, fruits, vegetables, cooked tomatoes, olive oil
Japan, China, Korea	High salt, cerebrovascular embolism, *Helicobacter pylori* and salted, pickled foods, stomach cancer. Japan developed continuing National program to reduce salt intake	Until recently, low risk for Western (US) diseases, but increasing in the last 15–20 years through adoption of Western nutritional habits (evidence for adverse effects of Western nutrition). High green tea intake, soy foods
South Asia		Mostly vegetarian tradition, with vegetables, fruits and starches, tea, but with milk (beneficial effect of tea not clear)

[a] CHD = coronary heart disease.

cidence of all cancers (18). In the United States, it is second after primary lung cancer (19). In the United States, there are differences as the function of race, and black males have a higher incidence and mortality compared with whites. Hispanics are intermediate (20). The reasons for these differences as a function of race are not yet clearly defined but inasmuch as this disease is very much related to dietary habits, it is likely that nutritional traditions in various populations are associated with risk and thus, the incidence. A recent article (21) reported a lower serum lycopene level in blacks, possibly accounting for the higher prostate cancer rate in blacks.

As noted, in people of the Mediterranean region with an above-average intake of vegetables and especially of cooked tomatoes, the incidence of prostate cancer is lower, probably the result of inhibition of two kinds of reactions involved in prostate cancer causation. The first reaction relates to the probable genotoxic carcinogens, most likely the heterocyclic amines formed during cooking of meat, especially of beef and pork (22). In the Mediterranean region, veal is the main meat consumed, and the cooking often involves a marinating fluid that keeps the meat from browning and thus, eliminates or certainly decreases the formation of heterocyclic amines (23). The second area deals with the type of oil used, which is usually monounsaturated olive oil (8–13). This oil has been shown not to promote the nutritionally linked cancers, including prostate cancer. Also, the dietary traditions involve the generous intake of protective vegetables and particularly of tomatoes.

As already noted, in relation to the etiology of chronic diseases, heart disease, many kinds of cancer and premature aging is the formation during cellular metabolism of reactive oxygen species, such as hydroxy radicals, peroxides, and peroxynitrite (16, 17). These reactive intermediates lead to the formation of oxidized LDL cholesterol, as regards coronary heart disease, and of oxidized nucleotides in DNA, such as 8-OHdG, found in tumor DNA. A key function of antioxidants, including lycopene in tomatoes, is to prevent these adverse oxidation reactions. Therefore, a major function of vegetables and fruits, soy products, and green and black tea is to provide the antioxidants to lower the formation of reactive oxygen species.

It is important to have markers for products associated with disease causation and those that act as chemopreventive nutritionals. It has been shown that individuals consuming well-done fried meat display some heterocyclic amines and mutagenicity associated with these chemicals in urine (22). It is possible, therefore, to determine the effectiveness of vegetables such as tomatoes in decreasing the presence of those indicators. It is expected that vegetables would increase the formation of detoxified metabolites, mainly C-hydroxy derivatives of the heterocyclic amines, found in urine as such or as conjugates formed by phase 2 enzymes.

Lycopene is naturally present as the *trans* compounds but during heating, the energy provides for the conversion to *cis* compounds, which are more lipid soluble and, therefore, are absorbed better as part of a diet including olive or canola oil. There have been metabolites of lycopene isolated, but it would seem that these are ineffective as antioxidants, for the most part. The European group coordinating research on antioxidants with emphasis on tomatoes in relation to health benefits has published a monograph (24).

There is epidemiological evidence that consumers of vegetables, including cooked tomatoes, have a lower risk of many types of chronic diseases, including heart disease and key types of cancer, such as cancer of the lung, breast, ovary, and intestinal tract, as well as a major effect on the prostate. In the latter case, there is a good marker in men, namely the prostate-specific antigen, which can be used to establish the benefits of specific items in the diet, such as tomatoes. For many of these cancers, there are good animal models that can be used to study the beneficial role of lycopene and tomatoes extracts and other dietary factors such as oils in reducing the incidence and mortality as a function of amounts consumed. In addition to prevention of carcinogenesis, tumor cells can be eliminated through the phenomenon of apoptosis, which may be increased lycopene.

In modern medical science, there have been arguments for establishing the value of a chemopreventive agent through clinical trials. Such studies are lengthy and expensive. The protocols need to be well designed with adequate control populations and adequate number of people involved to ensure statistical significance of results obtained. Another means that we favor are worldwide studies on disease incidence and mortality through the techniques of geographic pathology. Lifestyle traditions are diverse in different parts of the world. This is especially true for nutritional habits. Much can be learned also from changes in nutritional traditions, such as those unfortunately taking place in Japan, where people have westernized their dietary traditions, with increases of the nutritionally linked cancers, including invasive cancer of the prostate (2, 4, 7). Akazaki (25) performed serial sections of the prostate of old Japanese men and discovered carcinoma *in situ*, but rarely the invasive type, in contrast to Japanese in Hawaii, where more advanced lesions were observed (26). This effort led to the conclusion that the early events and thus, the likely carcinogens were similar in traditional Japan as in the United States, perhaps an exposure to heterocyclic amines from fried fish. However, there was no enhancement in Japan through the Western high-fat diet. The usual Japanese dietary habits were low in total fat but rich in vegetables, fruits, soy foods, and green tea. With the progressive Westernization taking place in Japan, there is an increased development of invasive prostate cancer and in fact, of the other Western nutritionally linked cancers (4, 7). The same unfortunate series of events are taking place in Italy, more so in Northern Italy (and, in fact, actually in many parts of the world). There is an influence of American dietary habits, facilitated by inexpensive fast food restaurants. Thus, fewer protective vegetables, including tomatoes, are consumed

and there is a rise of prostate cancer and of other Western types of cancer. The results described in this symposium suggest that the intake of cooked tomatoes and vegetables in general is a health-promoting tradition. It may be well to educate the public along those lines. In the United States, the federal government provides price support for certain foods to maintain or stimulate their production by farmers. It may be cost effective to encourage the same type of activity of price support for vegetable and fruits, including tomatoes, so that the consumer can buy these valuable health-promoting foods at a lower price facilitating to make them part of their regular diet. Sick people and disease care are expensive. Thus, having disease-preventing foods available at low cost is a good investment (27, 28).

The current symposium on tomato products and carotenoids in disease prevention provides an important series of articles that extend and update concepts and facts presented at a previous multidisciplinary interactive conference (29).

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