Evaluation of the Evidence on the Role of Tomato Products in Disease Prevention[1]

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Abstract. **During the last 30 years, research in the field of nutrition and chronic disease causation has led to exciting, significant progress in providing an understanding of specific risk factors and chemopreventive agents. The major health problems considered are cardiovascular diseases and the nutritionally linked cancers, including those in the stomach, colon, breast, prostate, ovary, and endometrium. The major elements considered were salt, type and amount of fat, and heterocyclic amines formed during cooking. Bran cereal fiber, as well as vegetables, fruits, and tea have been shown to inhibit the complex processes of initiation and development of these diseases. One aspect involved in initiation and development of both cardiovascular diseases and the cancers noted are abnormal oxidative processes leading to the generation of hydroxy radicals and peroxy compounds. In part, the protective role of vegetables, fruits, and tea is to provide antioxidant vitamins and specific polyphenols that display a powerful inhibition in oxidative reactions. Epidemiological studies as well as laboratory experimentation have yielded sound data and evidence in support of the fact that vegetables, fruits, and tea and specific antioxidants therein account mechanistically for inhibition. Geographic pathology has provided important data that populations with a regular intake of tomato products, such as in the Mediterranean region, have a lower incidence of the chronic diseases noted. The current Symposium is considering the varied mechanisms of action of tomato products in general, and one of the active principles, lycopene. Cooking is a factor in releasing the desirable antioxidants from tomatoes. Cooked tomato products may be preferable to the raw vegetable or juices derived from tomatoes bearing on absorption of the active principles. Optimally, absorption of lycopene, a highly lipid-soluble chemical, is improved in the presence of a small, but essential amount of oil or fat. Research in the field of nutrition and health has shown that monounsaturated oils such as olive oil or canola oil are most desirable, since such oils do not increase the risk of atherosclerosis, coronary heart disease, or the nutritionally linked cancers. The International Symposium on tea conducted in 1991 has provided worldwide interest in research on the beneficial effects of tea. It is now hoped that the present Symposium, dealing with another inexpensive and readily available food, tomatoes, will enhance interest in and funding for additional research, to underwrite future recommendations for possibly enhanced production and use of tomato-derived nutritional elements, with the goal of application to the prevention of major chronic diseases, the treatment of which is costly and often ineffective.** [P.S.E.B.M. 1998, Vol 218]

In the Western world, the major chronic diseases include cardiovascular diseases, the tobacco-related cancers such as cancer in the lung, pancreas, kidney, and urinary bladder, and those associated with nutrition such as those in the colon, breast, prostate, ovary, endometrium, and pancreas (1–3). In contrast, in the Orient the greatest health problems are hypertension and stroke and cancers in the stomach, esophagus, and liver (4, 5). In recent years, there

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has been an impressive collection of data on the lower incidence of mortality from major chronic diseases in the Mediterranean region, in particular in Southern Italy and Greece, countries for which there has been good epidemiological information (6–8). This paper deals with an analysis of the mechanisms accounting for the lower risk of the Western-type, chronic diseases in the Mediterranean region. In part, the beneficial effects are associated with dietary traditions involving the use of olive oil in the category of fats, of veal in the selection of meats, and of fish as sources of protein. Of great importance is the traditional frequent and considerable intake of fresh fruits and cooked vegetables, including a regular intake of cooked tomato products. The major starch is in the form of pasta and of bread made from whole grain flour. The organization of our documentation will be an evaluation of causative factors on the one hand, and of promoting elements on the other.

Causative Factors

Coronary Heart Disease. Sound documentation suggests that the early events in coronary heart disease stem from oxidized products of LDL cholesterol (9), and perhaps also from heterocyclic amines formed during cooking of meats during the browning reaction (10, 11). The traditional way of cooking meats in the Mediterranean region, mainly involving veal, does not generate appreciable amounts of heterocyclic amines. In contrast, the frying or broiling of red meats such as beef produce considerable amounts of heterocyclic amines, risk factors not only for coronary heart disease, but also for the nutritionally linked cancers such as cancer of the colon and breast. It is evident that nutritional factors rich in antioxidants provided by vegetables and fruits would inhibit the oxidation of LDL-cholesterol. A major role in this inhibition is played by lycopene, the key antioxidant in tomatoes and made readily available to the body from cooked tomatoes (12). Lycopene is highly lipophilic and its absorption is favored by the presence of fats, such as olive oil from the Mediterranean area.

Nutritionally Linked Cancers. These diseases include cancer of the distal colon and rectum, postmenopausal breast, pancreas, prostate, ovary, and endometrium. With the discovery by the group of Sugimura, Nagao, *et al.,* (10, 11) that frying or broiling of meats and fish lead to the formation of powerful mutagens, a new view on causative factors in the nutritionally linked cancers was generated. These mutagens were identified as a new class of chemicals, the heterocyclic amines. There are approximately 20 such compounds now known. Evidence is at hand that people who frequently eat meat well done have an elevated risk of colon and breast cancer (10, 11). It would appear that the procedures used in the Mediterranean region to cook meat and fish does not involve the browning reaction to any great extent, since these foods are cooked in the presence of sauces minimizing the formation of heterocyclic amines. This is especially so since the sauces frequently used involve cooked tomatoes, including lycopene, that would inhibit the formation of mutagens (unpublished observations). We did find such an inhibition by other antioxidants, such as those present in black or green tea (13).

Developmental Aspects

Cardiovascular and Neoplastic Diseases. The eventual occurrence of coronary heart disease is associated with occlusion of the vascular system by deposits including cholesterol. It has been shown that dietary cholesterol plays a minor role in this effect. Rather, it is the biosynthetic cholesterol, formed mainly in the liver, which is the major problem. The mechanism involves a dietary regimen rich in saturated fats that generate cholesterol associated with complex proteins (9). The key element is cholesterol associated with a protein leading to the excretion of LDL-cholesterol from the liver into the blood stream. Monounsaturated oils such as olive oil or canola oil yield lower levels of LDL-cholesterol. Also, the omega-3 polyunsaturated oils present in fish and in flax seed, among other foods, yield low circulating levels of LDL-cholesterol, indicating the value of consuming these types of foods frequently. On the other hand, the omega-6 polyunsaturated oils such as corn or safflower oil appear to induce liver enzymes that convert the cholesterol produced to bile acids, excreted into the gut. Thus, these oils also lower serum cholesterol, an apparent beneficial effect for lowering the risk of heart disease. However, bile acids are enhancing products that can contribute to cancer of the colon and rectum (2). These types of oils (like corn and safflower) also enhance the production of estrogen, in turn leading to a hormonal imbalance between pituitary, adrenal, and ovarian hormones and increasing the risk of cancer of the breast, ovary, and endometrium (2). Thus, olive oil stands out as a fat without adverse effects in relation to cardiovascular and neoplastic diseases. It is important to understand, however, that all fats and oils have more than twice the caloric availability than starches or proteins. This fact needs to be considered in avoiding obesity.

Vegetables and Fruits

These foods, so popular in the Mediterranean region, are good sources of the major vitamins. Many of them also provide other essential antioxidants such as quercetin, a polyphenolic antioxidant similar in chemical structure to polyphenols present in tea. It turns out, however, that tea is not consumed frequently in the Mediterranean region, but tea accounts for the lower risk of heart disease and cancer typically seen in the Orient, where tea has been shown to be beneficial (4, 5).

The Mediterranean diet customarily uses pasta as the major starch although rice is favored by some. These complex carbohydrates are sources of resistant starch that is incompletely hydrolyzed to available glucose in the intestinal tract (14). The consequence of the intake of these starches is lower caloric availability. They also act as a fiber in enhancing stool bulk. In turn, this exerts beneficial effects

in increasing the excretion of estrogen and related hormones, as well as of bile acids.

Pasta used in the Mediterranean area frequently involves the intake of cooked tomatoes and tomato sauces as seasoning and flavoring agents. The major antioxidant in tomatoes is lycopene, a chemical structurally similar to β-carotene (15). However, in contrast to the latter, lycopene is chemically quite stable to heat and cooking. Thus, under the conditions of practical cooking methods employed in the Mediterranean region, this important antioxidant is freely available, and its absorption is favored by the presence of olive oil because lycopene is quite nonpolar. In much of the world, except Asia, tomatoes are part of dietary traditions, especially so in Greece and Italy. In the United States, tomato and lycopene intake is increasing.

Lycopene lowers the oxidation of LDL-cholesterol and accounts in part for the lower risk of cardiovascular disease (9, 16). In addition, we discovered that lycopene also blocks the conversion of food mutagens found in fried or cooked meats and fish in the form of heterocyclic amines, and specifically the major product formed, namely 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine to reactive, mutagenic products (unpublished results). Also, as we indicated, these kinds of mutagens are present to a small extent in the usual Mediterranean diet, and these small amounts are not activated to reactive products leading to cancer or cardiovascular diseases through the favorable, inhibiting effect of antioxidants in vegetables, including tomatoes. Lycopene also is beneficial in increasing the availability of antioxidant potential in the body to lower the risk of adverse oxidative reactions generating hydroxy radicals and peroxides (17–19). Lycopene, unlike other carotenoids, failed to alter the levels of NAD(P)H: quinone reductase or glutathione-S-transferase in human colon cancer cells, Colo205 (20), although colon cells obtained from humans on carotenoid-rich diets did show the presence of lycopene, after a lag period (21). Also, smoking and alcohol affected plasma levels of some carotenoids, but not of lycopene (22). Plasma levels, in part, reflected intake of carotenoid- and lycopene-containing foods (23–25). There was an association between lycopene in plasma and in skin (26) but not between plasma lycopene and risk of skin cancer (27). Lycopene may protect against cancer of the cervix (28, 29), prostate (30–33; papers in this volume), colon (34, 35 and this volume), liver (36), but not breast (37), although lycopene, but not β-carotene, gave fewer chemically induced mammary gland tumors in rats (38). Ovarian cancer development was not affected by lycopene or other micronutrients (39). Lung cancer is lower in regular consumers of vegetables and fruits, but not specifically of lycopene (40–42). Cigarette smoke seems to lower availability of carotenoids (43). Yet, lung tumors were lower in mice on lycopene (44). Lycopene is a good inhibitor of cell proliferation (45), so the different effects observed under various conditions could be determined by the locally available concentration. Several reviews critically assess dietary vegetable, tomato, and lycopene intake in heart disease and cancer prevention (15, 46–48). Other reports at this Symposium show that lycopene is well distributed in most tissues of the body. Therefore, its beneficial effects would be broadly available in decreasing risks of disease stemming from specific oxidation reactions and products.

Conclusions

Within the framework of Western dietary traditions, the Mediterranean dietary habits clearly provide a lower risk for developing the major chronic diseases such as coronary heart disease and many types of cancer. We have analyzed the multiple factors accounting for this beneficial effect in terms of the mechanisms of disease causation and development. The antioxidant lycopene, present mainly in tomatoes, and available optimally in cooked tomatoes as consumed in the Mediterranean region together with olive oil, is one key factor accounting for increasing the biochemical and molecular defense mechanisms usually associated with protection against metabolic reactions leading to heart disease and cancer. Lycopene decreases the formation of oxidized products of LDL-cholesterol and those derived from heterocyclic amines produced during cooking. Lycopene also diminishes the occurrence of products of active oxygen, including hydroxy radicals and peroxides, and may lower cell cycling. Clearly, nutritional habits providing a good source of lycopene, and also of olive oil to facilitate its ready absorption and availability to tissues, clearly deserve emphasis in terms of achieving healthy lifestyles and disease prevention, the definite means of disease control.

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