Summary of the Round Table Discussion on Strategies for Cancer Prevention: Diet, Food, Additives, Supplements, and Drugs

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Abstract

A Round Table Discussion was held at the Fourth International Conference on Anticarcinogenesis and Radiation Protection. Scientists from government and academia were brought together to discuss the evidence for the preventive effect of foods, specific nutrients and drugs against cancer, and the most appropriate methods of initiating nutritional cancer prevention activities to improve the health of the public. The panel reviewed the epidemiological evidence of the role of diet and specific micronutrients for the prevention of cancer, the doses of specific micronutrients required for preventive effects and their safety, the evidence for aspirin as a chemopreventive agent, the issue of foods versus specific micronutrients in the prevention of cancer, food safety, and approaches to prevention such as food fortification or dietary supplements. The remarks of the panel members are summarized.

The Role of Foods and Specific Micronutrients in the Prevention of Cancer: The Epidemiological Evidence (Dr. Helzlsouer)

Rates of cancer differ by geographic region nationally and internationally, and marked changes in the rates of some cancers in the U.S. have occurred over this century (1-3). The marked geographical differences, alteration of cancer rates with migration, and the changes in rates within countries over relatively short time periods indicate a strong contribution by environmental factors.

The two major contributing environmental factors are smoking and diet (4). Approximately 30% of all cancers and 90% of lung cancers can be attributed to cigarette smoke (4). Smoking prevention and smoking cessation are the best known proven methods of preventing cancer. Estimates of the contribution of diet to cancer are less certain and range from 10 to 70% (4). Evidence continues to emerge regarding the role of dietary patterns, such as high fat and low fiber diets, as well as the influence of specific nutrients in the etiology of or protection against cancer. Specific nutrients such as the carotenoids, vitamins E, A, and C have been shown to be protective against many cancer sites. Summaries of serum bank studies investigating the association between prediagnostic serum vitamin E and beta-carotene levels and the development of specific cancer sites are presented in Fig. 1 and 2 (5). For vitamin E, cases tended to have lower levels before diagnosis compared to controls, for several cancer sites, but the differences are small (Fig. 1). Few of the studies showed a statistically significant difference. Serum beta-carotene appears to be protective against several epithelial cancers, particularly lung cancer (Fig. 2).

The cancer preventive effect of a multitude of specific food components continues to be investigated through animal studies, human observational studies, and clinical trials. In evaluating the benefit of specific nutrients in human observational studies, the question remains of whether the specific nutrients themselves are protective or if something else in the diet, closely associated with the nutrient intake, is protective. Many dietary studies show protective effects for dietary patterns rather than specific micronutrients.

The epidemiological evidence to support the benefits of fruits and vegetables and specific nutrients is accumulating at a rapid pace. An article in the New York Times on April 13, 1993 highlighted the potential cancer fighters in food (6). The extensive list of potential cancer preventive micronutrients in foods include the carotenoids, vitamin C, vitamin E, flavonoids, and fiber. The remaining question is how to best improve the population’s cancer preventive nutritional status, through encouraging consumption of foods rich in these specific micronutrients or through dietary supplements of specific micronutrients? In this pill-taking society, many look for the magic pill to prevent cancer. The conclusion reached by Ms. Natalie Angier in the New York Times Article warns against this search for the quick fix. She states “...the intricacy and synchronicity of the chemicals in

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1 Present at the 4th International Conference on Anticarcinogenesis & Radiation Protection, April 18-23, 1993, Baltimore, MD.

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plants argue firmly against an undue reliance on vitamins and supplements to compensate for a rotten diet of snacks and french fries. If scientists have yet to understand all the subtleties of a Brussels sprout, how can anybody hope to recapitulate it in a pill?" (6). The approach favored by the National Cancer Institute is embodied in their campaign to promote the intake of five servings a day of fruits and vegetables for the prevention of cancer. However, the difficulty in achieving this on a daily basis may argue for a combined approach of dietary sources and supplements.

The health of the public requires an open discussion of the best method(s) of achieving a healthy diet. Approaches include shifts in dietary patterns to eating a higher proportion of fruits and vegetables in the diet, fortification of foods such as the what has been done with milk, and vitamin supplementation. The variety of nutrients with potential cancer preventive properties, as well as the undiscovered cancer preventive constituents of foods, argues against a supplement-only approach to enhancing health.

**Safety Issues of Vitamin Supplements (Professor Diplock)**

Vitamin E is a remarkable molecule, and we should perhaps remind ourselves that God actually made the tocopherols to enable plants to protect their chloroplasts from oxidative damage; it is perhaps something of a metabolic accident that we, as mammals, have actually learned to avail ourselves of this protection!

I wish to address two points in this general comment. The first is the question of the validity of the concept of RDA for the antioxidant nutrients, vitamins E and C (in its antioxidant role), and the carote-

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3 The abbreviations used are: RDA, Recommended Daily Allowance; NSAIDs, non-steroidal antiinflammatory drugs; FDA, Food & Drug Administration.

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noids, notably β-carotene. My view is that the concept of RDA for the antioxidant nutrients is flawed. The RDA was a concept that was developed for the water-soluble vitamins and was related to clearly definable human vitamin deficiency diseases. No such deficiency diseases exist for vitamin E, for vitamin C in its antioxidant role, or for β-carotene. For the water-soluble vitamins, the RDA relates to the amount of the nutrient required to prevent the deficiency disease, and, since it is clearly known what the role of the vitamin is as an enzyme cofactor, it is easy to understand how a quite sharp cut-off point can be established between deficiency and sufficiency. Once the cofactor site of the enzyme is saturated with the cofactor in question, then no further biological advantage can be expected to occur if the intake is increased. Considering the known biological role of vitamins C and E and β-carotene as antioxidants, there is no such cofactor relationship. Over a sensible range of values, an increase in amount of intake can be expected to result in biological advantage (Fig. 3). The question of the range of intake within which biological advantage can be expected is the real question, and the need for consideration of this key question is frequently hampered by slavish adherence to the RDA concept. I suggest that there is a great need for a fresh look at this concept, based on the principles that I have outlined above.

My second point, which is of vital importance in considering the potential clinical efficacy of increasing the intake of the antioxidant nutrients, is their safety. The question as to the possible dangers of advocating increases in intake must be answered unequivocally, and a firm positive statement as to the safety of vitamins C, E, and β-carotene can be made with confidence. With respect to vitamin E, Professor Herman Kappus and I have recently published an extensive review of the literature of human vitamin E safety (7). We were able to state, with a high degree of confidence, that the toxicity of vitamin E is very low. The reported increases in serum lipid levels following a high dose of vitamin E were anecdotal and highly inconsistent. In the several double-blind trials that have been carefully done, there was no evidence at all of changes in serum lipid levels. Animal studies showed that vitamin E is not mutagenic, carcinogenic, or teratogenic. In double-blind human trials with large and very large (3g per day orally for 9 weeks) doses of vitamin E, there were no consistent side effects, although some minor gastrointestinal disturbance was noted in some cases. We concluded that, for pharmacological purposes, dosage up to 1.5 g per day orally can be considered to be completely safe. This dose is more than 10 times the intake which has recently been shown to be associated with a lowered risk of cardiovascular disease in men and women (8, 9). One word of caution should be mentioned; high oral intake of vitamin E may exacerbate the blood coagulation disorder of vitamin K deficiency caused by malabsorption or anticoagulant therapy, and high levels of vitamin E intake are, therefore, contraindicated in these subjects.

With respect to β-carotene, a careful review by Dr. Adrienne Bedich (10) similarly concludes that β-carotene is very safe. β-Carotene has been successfully used to treat inherited photosensitivity disease for 20 years at doses of around 180 mg per day orally without any adverse side effects being reported apart from hypercarotenodermia, the phenomenon of the skin turning a rather rich shade of orange. Toxicity studies in animals have shown that carotene is not mutagenic, carcinogenic, or teratogenic; it does not cause hypervitaminosis A because the conversion of β-carotene to vitamin A is dependent on the vitamin A status of the individual, which if adequate, limits the uptake of carotene and its conversion to vitamin A. Thus, even when the oral intake of β-carotene is high, there is little increase in the circulating level of vitamin A. In a few isolated reports that claimed to carotenoid-related toxicity, the apparent toxicity was probably caused by other constituents of the carotene-rich food and not by the carotene itself.

With respect to vitamin C, I am unaware of any double-blind toxicity study. However, it is well known that many individuals take supplements of this vitamin in megadose quantities without apparent harm.

In Situ Kinetics: Biochemical and Clinical Interface to Determine Vitamin C Requirements (Dr. Levine)

Humans and other primates lack the gene product for gulonolactone oxidase, which is necessary for ascorbic acid (vitamin C) synthesis. Since we cannot make ascorbate, we must ingest it. How much should we ingest? The current approach utilizes the guidelines of the RDA for ascorbate; the RDA is 60 mg.

The RDA for ascorbate has three goals (11). The first is to prevent signs and symptoms of scurvy, the vitamin C deficiency disease. The RDA was chosen to both prevent and cure scurvy. The second basis is to provide adequate reserves. The RDA was chosen to provide approximately a 1-month reserve against scurvy. The third goal is to replace catabolic losses.

There is no doubt that the RDA will prevent scurvy. However, a key issue is whether preventing deficiency is equivalent to optimal intake. Simply stated, minimal may not be equivalent to optimal. Other problems with the premises of the RDA (12) include the methods of determining adequate reserves and catabolic losses, and, most importantly, that ascorbate requirements are not based on function of the vitamin.

Ascorbic acid is an electron donor, a reducing agent. The mechanism of vitamin C action is by donating single electrons or two electrons together. By this means, ascorbate participates in a variety of
enzymatic and nonenzymatic (chemical) reactions. What is missing from vitamin C requirements is knowledge of how different amounts of the vitamin regulate its function. Instead of using prevention of deficiency as an end point, vitamin requirements should be based on what the vitamin does in relation to its concentration. Both enzymatic and nonenzymatic functions can be studied to obtain this dose response or kinetic information. However, the functions must be studied, not simply as isolated reactions, but for reactions in situ. In situ specifically indicates that the reactions should be studied in place in cells, organelles, tissues, whole animals, and eventually humans. The underpinnings of this approach to vitamin requirements are truly functional, and the concept is called in situ kinetics.

The hypothesis of in situ kinetics has been verified in many experiments in animal tissue (13). These experiments indicate that kinetics for ascorbate-dependent enzymatic reactions can be determined in situ and that the action of vitamin C is different in situ compared to isolated reactions.

In situ kinetics has two broad components (13). One component is biochemical. The goals are to determine the reactions in which ascorbate is a participant in situ, how the reactions can be measured in situ, how ascorbate concentration can be varied over a wide range, and ultimately, how in situ reactions are regulated by ascorbate concentration.

The second component of in situ kinetics is clinical. The goals are to learn what concentrations of vitamin C can be achieved in people as a function of vitamin dose and whether concentrations are achieved in humans which regulate the biochemical reactions in situ i.e., a dose-response curve for ascorbate must be determined.

We designed an inpatient clinical study at the NIH to investigate the in situ kinetics of vitamin C. Normal healthy volunteers are recruited to live in the NIH Clinical Center for 4–6 months and are provided a diet containing less than 5 mg of ascorbic acid daily.

The purpose of the first phase of the clinical study is to reduce plasma ascorbic acid to very low amounts but without signs or symptoms of deficiency. The target concentration for ascorbate depletion is 5–10 μM. When target depletion concentration is achieved, participants begin the second phase of the clinical study, repletion of ascorbic acid at increasing doses. Bioavailability testing is performed for the first ascorbate dose. Fifteen mg ascorbic acid is given by mouth, and blood samples are taken every 30–120 min for the subsequent 24 h. At this time, the same dose of ascorbic acid is given i.v., and blood samples are taken for the next 12 h. From these data, the concentrations achieved from oral absorption can be compared over time to the concentrations from i.v. administration; these data indicate bioavailability by definition. Twenty-four-h urine samples are also collected to measure urinary excretion of ascorbate, oxalate, urate, and creatinine.

Participants are begun on oral ascorbic acid 15 mg by mouth twice daily for a total dose of 30 mg. Ascorbic acid is given in the fasting state so that pharmacokinetic analyses can be performed.

Participants remain on the 30-mg dose until a plateau concentration in plasma is achieved. A plateau concentration is defined by a ≤ 12% SD of mean concentration levels among samples drawn on a minimum of 5 different days over at least 1 week’s time. At plateau, participants undergo apheresis to obtain monocytes, platelets, plasma, and lymphocytes. Additional blood is taken to isolate neutrophils, and male volunteers are asked to provide semen samples. The ascorbate dose is then increased, and the procedures are repeated. The doses given in sequence are: 30, 60, 100, 200, 400, 1000, and 2500 mg. At each dose, a plateau concentration is determined in plasma and tissues, which can then be expressed as a function of dose. In this way, the first complete dose-response curves relating ascorbate ingestion to ascorbate concentration will be determined. These data will be essential to determine human ascorbate requirements using the principles of in situ kinetics.

One potential objection to this study is that there could be great variability in different people in their response to ascorbate doses. It is possible that there are inherent genetic differences in ascorbate absorption in humans. Sources of variability, other than genetic variability, are controlled by providing all food which is depleted of vitamin C, giving ascorbate only as a drug, and measuring vitamin C by an ultrasensitive assay developed at the NIH, which solves the problems of sample instability and interfering substances. If, despite these measures, responses to a given dose vary widely, the dietary recommendations and dose-response information will use data from those subjects with the lowest absorption.

To this time, seven men have enrolled in the study, and five have completed it. Males were selected because males volunteered for the study, for unclear reasons. Women will also be enrolled in the study, once they can be recruited.

The interface of clinical in situ kinetics with biochemistry should provide a quantitative and functional basis for ascorbate requirements in humans.

Mechanisms of the Protective Effect of Nutrients and Determination of Optimal Nutrient Intake (Dr. Blumberg)

The modern paradigm of nutrition focuses on the ability of diet and its nutrient and nonnutrient components to reduce the rate of loss of physiological functions leading to chronic diseases associated with aging. Evidence is available that essential nutrients may beneficially affect several of these age-related changes, e.g., calcium and vitamin D may reduce impaired bone remodeling and the risk of osteoporosis; vitamin E and β-carotene may slow the oxidative modification of low-density lipoprotein cholesterol and the development of atherosclerotic lesions; and vitamin C may delay the denaturation of eye lens protein and the occurrence of cataracts.

The contribution of diet and nutritional status to cancer risk and, conversely, to the prevention and treatment of cancer, has been a major focus of research as well as public health policy. Despite the compelling research evidence available today, it is clear that most Americans do not follow guidelines consistent with dietary recommendations to reduce the risk of cancer. These guidelines emphasize diets with generous servings of fruits and vegetables and high fiber foods as well as foods low in fat and rich in vitamins A and C. Whereas a large body of epidemiological studies consistently affirm that low intakes of fruits and vegetables and carotenoids and vitamin C are associated with an increased risk of several types of cancer, questions remain about the nature of the full dose-response relationship extending to supradietary intakes. Recent studies provide some intriguing evidence that optimal nutrient intakes for the prevention of chronic diseases may be most readily achieved via food fortification and/or nutrient supplementation.

Nutrients may exert their protective effect against carcinogenesis through several mechanisms. Preventing initiation is one critical strategy as once a cell is initiated, the damage is irreversible for that cell. Thus, identification of nutrients which detoxify carcinogens and/or block their actions before they damage DNA represents an important area of investigation. The damage to DNA produced by oxygen radicals is extensive and appears to contribute significantly to the carcinogenic process; antioxidant nutrients appear to modulate this event. Dietary antioxidants can act to block direct oxiradical attacks on DNA and also serve to impede the production of toxic intermediates from epigenetic targets such as aldehydes and chloramine generated through lipid peroxidation events and other oxidative reactions.
Opportunities also exist for nutritional interventions which inhibit cancer at the later stages of promotion, conversion, and progression. Recent investigations continue to add support that generous dietary or supplemental intakes of certain micronutrients reduce the risk of cancer. Epidemiological studies suggest that vitamin D and calcium exert a protective effect in cases of colorectal cancer. High plasma levels of vitamin A have been determined in prospective and retrospective investigations to be associated with a lower risk of lung, kidney, and other cancers. Experimental data indicates that the anticarcinogenic action of vitamin A may occur at the level of differentiation and antipromotion, including maintenance of intercellular communication through gap junctions.

Folic acid deficiency favors the onset of malignant transformation of cells via several mechanisms including dysregulation of the supply of methyl groups necessary for DNA methylation, which in turn is a major determinant of histone binding, chromosome structure, and gene transcription. Clinical interventions as well as epidemiological studies have shown an association between low folate status and increased risk of dysplasia or cancer of the cervix, colon, bronchus, and esophagus. Folate supplementation has been reported to reduce the incidence of dysplasia and cancer in patients with chronic ulcerative colitis.

Establishing appropriate criteria for nutrient intakes which reduce the risk for cancer present researchers and public health officials with a difficult challenge. It remains important to consider the many influences which impact on specific nutrient requirements for disease prevention, including the interactions with other nutrients and nonnutrient components of foods as well as environmental pollution, genetic determinants, and even the process of aging. Clinical trials to determine these relationships must use the most appropriate biomarkers for cancer as well as more traditional disease end points. This approach will present opportunities for developing and implementing sound dietary guidelines and rational nutrient supplementation for chemoprevention and adjacent nutrition therapies for cancer treatment (selected Refs. 14–22).

Aspirin and Related Non-Steroidal Antiinflammatory Drugs as Chemopreventive Agents against Colon Cancer (Dr. Marnett)

Reports from Thun et al. (23), Kune et al. (24), and Rosenberg et al. (25) suggest that aspirin intake may reduce colon cancer incidence (24, 25) and mortality (23) in the general population. Aspirin is a relatively specific inhibitor of the cyclooxygenase branch of the arachidonic acid cascade and a member of a series of compounds known as NSAIDs. NSAIDs share a common biochemical mechanism of action, which raises the possibility that other compounds beside aspirin may be chemopreventive for colon cancer (26). This is an exciting possibility because there is an enormous base of clinical experience with NSAIDs in humans. A variety of over-the-counter and prescription medications exist that could be entered into chemoprevention trials almost immediately. Furthermore, recent biochemical findings raise the possibility that the next generation of NSAIDs may not possess the gastric ulcerating activity of the currently available compounds, including aspirin. If these second generation NSAIDs retain the ability to inhibit the development of colon cancer, potent chemopreventive agents would be available with relatively few limiting side effects.

The pharmacological effects of NSAIDs derive from their ability to alter arachidonic acid metabolism (26). Mobilization of arachidonic acid from cellular phospholipids is linked to signal transduction pathways that result in the activation of phospholipase C and phospholipase A2 (27). Once arachidonic acid is released from phospholipids, it is oxidized by one of three different oxygenases, one of which is called cyclooxygenase. Cyclooxygenase is a membrane-bound hemoprotein that is widely distributed in mammalian tissue but not present in all cell types. It introduces two molecules of O2 into the carbon framework of arachidonic acid to form a hydroperoxy endoperoxide called prostaglandin G2. Prostaglandin G2 undergoes further transformations to produce a variety of bioactive lipids such as prostaglandins, thromboxane, and prostacyclin. Each of these metabolites exerts its own range of biological activities. With regard to cancer, certain eicosanoids stimulate or inhibit cell proliferation, enhance or retard tumor cell metastasis, and depress the immune response (28).

Cyclooxygenase is inhibited by aspirin and other NSAIDs. The best known of these are aspirin, indomethacin, ibuprofen, piroxicam, and sulindac. Aspirin is a competitive inhibitor and also covalently modifies the cyclooxygenase protein whereas indomethacin, ibuprofen, piroxicam, and sulindac are competitive inhibitors that do not bind covalently to the protein.

In rat models of colon carcinogenesis, cyclooxygenase inhibitors such as indomethacin, piroxicam, and sulindac exhibit chemopreventive effects. Sulindac has been reported to decrease the number of mice with dimethylhydrazine-induced colon tumors and the number of tumors per animal when administered in the diet throughout carcinogen administration.

Sulindac reduces the size and number of rectal polyps in individuals with familial polyposis (29). When sulindac administration is discontinued, the tumors recur, and resumption of sulindac treatment causes regression. The cyclooxygenase inhibiting effect of sulindac is due to its reduced form, sulindac sulfide; sulindac is reduced in the colon by bacterial microflora.

A significant unknown regarding the use of aspirin as a chemopreventive agent in colon cancer is dose. In the epidemiological studies (23–25), aspirin intake was estimated by questionnaire and reported as the frequency of ingestion. In a study by Paganini-Hill et al. (30), daily aspirin intake did not alter the risk of colon cancer whereas in the study by Rosenberg et al. (25), an aspirin intake on 4 or more days per week (“regular use”) was associated with a halving of colon cancer incidence. In the study by Thun et al. (23), colon cancer mortality decreased with increasing frequency of aspirin use. No frequency of aspirin intake was reported in the study by Kune et al. (24).

Occasional aspirin use is believed to be beneficial for prevention of cardiovascular disease, but there is still some uncertainty about the optimal dose. One adult aspirin every other day is protective against fatal myocardial infarction, but it is unknown if this dose would be protective against colon cancer. In fact, there is reason to believe it would not. The beneficial cardiovascular effects of aspirin derive from its ability to irreversibly inactivate cyclooxygenase in platelets (31). The ability of platelets to synthesize the vasoactive agent, thromboxane A2, is eliminated by a single aspirin dose. Renewed thromboxane A2 synthesis must await synthesis of new platelets, a process that requires several days. However, in epithelial cells, cyclooxygenase replacement occurs within a few hours following aspirin treatment; therefore, its duration of action is relatively short. There is no evidence to suggest that platelets contribute to the genesis of colon cancer; therefore, one would not expect a dose of aspirin that is effective at preventing cardiovascular disease to prevent colon cancer.

Recently, several groups have reported the detection of a proliferation-associated gene that is a novel form of cyclooxygenase (cox-2). Subsequent studies of this mitogen-induced cyclooxygenase indicate that it is sufficiently different in structure from the product of the constitutively expressed gene (cox-1) to permit the development of isoenzyme-selective inhibitors. The form of cyclooxygenase responsible for prostaglandin synthesis in the stomach appears to be cox-1,
and inhibition of this form by NSAIDs leads to gastric ulceration. A cox-2-selective inhibitor would be expected to inhibit prostaglandin synthesis without exhibiting ulcerogenic activity, which is the major limiting side effect of NSAIDs. If cox-2 is the form of cyclooxygenase responsible for prostaglandin synthesis in the colon, these selective inhibitors might be expected to be very effective chemopreventive agents against colon cancer.

The above discussion highlights the potential of NSAIDs as chemopreventive agents and underscores the importance of a precise understanding of molecular details of pharmacological action in drug development. The latter consideration emphasizes the importance of collaboration with the pharmaceutical industry for development of the next generation of chemopreventive agents. The pharmaceutical industry has the ability to take a lead compound and make a large number of analogues in a very short period of time. They have the ability to determine clinical pharmacology, toxicology, and efficacy, the properties that will determine if an agent can be useful in humans.

Issues of Food Safety (Dr. Schulplein)

I am presenting today as a regulator and a scientist. When discussing the risk or benefits of foods, supplements, or fortification of foods, consideration must be given to food safety. Most of the standards related to food safety that the FDA has go back to an Act that was passed in 1938. In 1938, ordinary, wholesome food was considered “safe.” There was no thought of interfering with the traditional food that people ate, or with the pattern of their diet, or the amount of fat, fruit, vegetables, or vitamins they consumed. The statutes that we enforce today take the position that ordinary food, cooked at home, is perfectly healthy and that the things that make it unsafe, or that might make it unsafe, are the commercial processing it receives or the synthetic additives, and the pesticides and contaminants we add to it.

The range of government intervention in the food safety area has been one of curtailing use or banning specific nonessential substances, not of providing information regarding possible hazards in the traditional diet or the patterns of the diet. Whatever their effectiveness over the years, I think that some of these statutes now tend to inhibit the speed and extent to which the FDA attends to new scientific data and incorporates it into public health information or into more useful food safety standards.

I’d like to make two major points. The first concerns the contribution of diet to cancer, a major cause of death. Basically what I’ve done is looked through the 1992 statistical abstracts and ranked the major causes of death in this country. The first is heart disease, and the rate of death is approximately 1 in 3. Cancer is second, 1 of 4.3 on a life time basis. Stroke is third at 1 of 15. Doll and Peto (4) estimated the attribution of cancer mortality to various causes. They argue that there are two major causes of cancer, cigarettes and diet. To many, the large attribution to the diet is a startling finding. This is still short of proof and remains controversial; however, the 1982 NAS Report on Diet, Nutrition and Cancer (32) concluded that “...it is highly likely that the United States will eventually have the option of adopting a diet that reduces its incidence of cancer by approximately one-third...”

The second point is that for the last three decades or so we have tended to emphasize the risks, both perceived and real, from synthetic carcinogens in food, the intentional additives and pesticides and the unintentional contaminants as well. This emphasis on synthetics has tended to distort our view of what we actually consume. Foods contain natural carcinogens in addition to what may come from exogenous sources such as pesticides. Based on food consumption patterns and data on naturally occurring carcinogens and pesticide residues and contaminants in foods from Bruce Ames and the FDA total diet survey, it is estimated that virtually all the food-borne carcinogenic risk comes from natural carcinogens contained in foods (33). Regardless of how we do risk assessment, most of the risk comes from traditional food, not synthetic additives or contaminants.

One of the challenges faced is to present the work that is done in food safety in a way to gain the attention of the public and government. We need to understand better the role of dietary modulation of carcinogenesis. The control of dietary risk from natural carcinogens would be enormously more useful to human health than regulatory efforts devoted to eliminating traces of synthetic residues or contaminants.

Importance of Foods in the Prevention of Cancer (Dr. Spence)

Much research has been conducted to identify naturally occurring compounds that can act to modulate carcinogenesis and hopefully prevent the incidence of cancer; clearly, much more research in this important area is needed. While there is a need to identify such compounds, there is, however, a tendency for the American public to be excessively interested in taking dietary supplements as a means to decrease their risk for cancer. While the goal of avoiding cancer is certainly most desirable, this approach may not be the most advantageous. It is important to realize that a supplement of any nutrient or nutrients against the backdrop of a poor diet can hardly be expected to produce the desired outcome. A more appropriate approach is one in which the importance of foods in the diet is stressed. The real challenge is to determine what is a healthy diet or what is a diet that most effectively can prevent the occurrence of cancer in an individual.

It is so obvious that it is often overlooked that our diet is made up of foods and that those foods are made up of individual nutrients. It is easy to lose sight of this, but it is important not to do so because the many components of foods have significant interactions among themselves or other components present in foods. While we know much about the function of the major nutrients, there are many compounds in foods that we do not have a clear understanding of their biological importance.

The relationship between diet and cancer is believed to be strong, although the exact relationship and the actual magnitude of the relationship is not clear. If one looks at the occurrence of many types of cancer and the relationship with overall diet, there tends to be a strong agreement. However, as a general statement as outlined in Fig. 4, when much of the data is examined more closely and correlations are looked at between individual foods, the correlations tend to be less convincing. Taking it a step further and looking at the relationship between cancer incidence and individual nutrients, the association is even less clear. As one examines the relationship between diet and cancer, there is a gradient in the reliability of the information as one begins to narrow down the particular nutrients involved. One possible explanation is that we simply do not know all of the important nutrients that are present in foods.

A case in point is vitamin A status and cancer. Earlier studies have indicated a relationship between the ingestion of vegetables in the diet and a lowered incidence of cancer (34). More recent studies have indicated that β-carotene may have a protective effect independent of...
its ability to provide vitamin A (35). Although it is now the subject of intense discussion, it may be premature to state that β-carotene is a cancer protective agent. It may turn out that that is the case, but it is still not clear since this particular carotenoid is only one of a very large number of carotenoids that occur in fruits and vegetables, many of which we cannot measure adequately. It may in fact be that β-carotene is actually only a good marker for the ingestion of fruits and vegetables, or that the one or several of the other carotenoids may actually have more of an effect on carcinogenesis.

The carotenoids are just one example. In Table 1 is listed a number of different classes of chemical compounds that may have biological activity in the prevention or causation of cancers. The list is not all inclusive but is presented to show the variety of different types of molecules that may be of importance. Some of these compounds have been shown to affect carcinogenesis in experimental model systems (36). Others may have no effect, may have very specific effects, or may have general effects such as acting as antioxidants. The actual mechanism of the biological activity, if any, of these compounds requires further study. In addition, there can be a number of other compounds that might exist in abundance or in trace amounts in foods that may have a protective effect in terms of carcinogenesis. The point is that we do not know enough to make specific recommendations about specific nutrients to do so with confidence. We do, however, have information that would suggest that foods that are rich in these classes of compounds, particularly fruits and vegetables, should be consumed in greater quantities. Such a suggestion will be of greater immediate benefit to the population at large than the more difficult task of identifying single nutrients that can then be used as dietary supplements.

The Case for Food Fortification (Dr. Block)

We are at the threshold of something that’s very much like a second revolution, a change in our understanding of nutrition and its relationship to disease, that oxidative damage and antioxidant nutrients are centrally important. We are at the threshold of this transformation because the epidemiology and the laboratory sciences are pointing to the same answer: that a build-up of oxidative damage is associated with increasing disease risk; and the possibility exists to affect that risk through the antioxidant defenses that come through a high intake of antioxidant nutrients.

There are hundreds of epidemiological studies of fruits and vegetables in cancer prevention, and the data are very consistent. Of the 200 studies of fruits and vegetables at about 15 cancer sites, 156 reported relative risks (37). Of these 156 studies, 128 found statistically significant reduced risks; you would expect three or four if chance alone was operating. A review of a few sites will give a sense of the consistency of the data. For stomach cancer, 14 of the 15 studies have found statistically significant reduced risk with high intake of antioxidant-rich fruits and vegetables. People in the low one-fourth of the distribution of intake had about twice the risk of developing stomach cancers as people in the upper one-fourth of the distribution. There appears to be an association between high intake of vitamin C, or something that comes along very closely associated with vitamin C, and reduced risk of cervical, oral, esophageal, and several other cancer sites.

What about antioxidants and breast cancer? Howe et al. (38) performed a meta-analysis of 12 case-control studies of diet and breast cancer. They found that vitamin C-rich fruits and vegetables had the most consistent and statistically significant inverse association with breast cancer, independent of the effect of dietary fat.

Part of the problem in the way we’ve been thinking about nutrients in relationship to cancer is that we’ve been arguing with each other and saying, “No, it’s not vitamin C, it’s β-carotene.” Or, “No, it’s not β-carotene, it’s vitamin C.” We need to acknowledge that it’s a variety of nutrients acting at different sites and through different mechanisms.

People always say, “Well, a lot of these things are tantalizing, but shouldn’t we wait for clinical trials?” I very much approve of clinical trials. But they will give us a small number of limited and specific answers to limited and specific questions. Most of the trials currently under way are in precancerous conditions, so they will only be questionably generalizable to prevention in people who don’t have any precancerous conditions. Most of the β-carotene studies are being done with 30 mg of β-carotene. This won’t tell us anything about 10 mg of β-carotene, or about other levels achievable in the diet, or about combinations. Maybe the combination of vitamin C and vitamin E is better than any one of them alone. We don’t have enough money or time or resources to engage in the kind of effort that will give us definitive answers to what combinations at what dose levels are effective in human populations. So yes, we should be doing clinical trials; they will give us some definite answers. But we are never going to have answers to whether dietary levels or combinations of antioxidants are protective even for the common diseases, let alone for most of the less common diseases.

We are seeing strong associations between diet and cancer. Where should we put our efforts? The National Cancer Institute is promoting five fruits and vegetables a day. I absolutely approve of that. There are lots of things in fruits and vegetables that you can’t get in a pill and never will. But, on any given day, only 60% of the population has even one serving of any fruit or fruit juice in the U.S. Only about 30% has even one serving of a fruit or vegetable rich in vitamin C or vitamin A. Only 9% of the population on any given day has that five servings of fruits and vegetables.

I approve of educating people to eat their five fruits and vegetables a day, but I think it is a public health mistake to say that’s the only way to go. That isn’t the way we wiped out rickets, or beriberi, or pellagra, or goiter. We wiped those out, not by telling people they ought to eat better, but by fortifying the food supply. And that’s what I think we ought to do now.

We ought to be moving toward fortifying the food supply with antioxidant micronutrients and backing away from our position that you don’t need and shouldn’t take supplements. As we said earlier, there really isn’t any substantial evidence that antioxidant nutrients are harmful, and there is substantial evidence that they may be helpful. In the context of health care costs, we need to prevent. This is cheap insurance for prevention. We ought to have economic policies that make these foods cheaper and health policies and food fortification that make a higher antioxidant level available to all members of the population.

References

Summary of the Round Table Discussion on Strategies for Cancer Prevention: Diet, Food, Additives, Supplements, and Drugs

Kathy J. Helzlsouer, Gladys Block, Jeffrey Blumberg, et al.

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