Chapter 1. Introduction

Purpose

Patients with cancer commonly try a variety of nontraditional treatments that fit the broad category known as Complementary and Alternative Medicine (CAM). However, evidence is lacking for the effectiveness of most CAM therapies for cancer. Among the CAM therapies publicized by the popular press for cancer treatment are several dietary antioxidants: vitamin C, vitamin E, and coenzyme Q10.

The purpose of our study was to conduct a systematic review of the scientific literature to identify and assess the evidence for the efficacy of these three antioxidants for the prevention and treatment of cancer.

Specific Aims

The National Center for Complementary and Alternative Medicine (NCCAM) and the Agency for Health Research Quality (AHRQ) established four specific aims for this study:

1. To identify all study reports on the efficacy of antioxidant supplements vitamin C, vitamin E, and coenzyme Q10 for preventing cancer;
2. To identify all study reports on the efficacy of antioxidant supplements vitamin C, vitamin E, and coenzyme Q10 for treating cancer;
3. To determine if sufficient evidence exists to recommend further study of these therapies;
4. To recommend the types of future research studies needed.

A Brief Review of the Use of CAM for Cancer Treatment

Antioxidants and Cancer

The April 2000 National Academy of Sciences/Institute of Medicine/Food and Nutrition Board report entitled *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* defined the term dietary antioxidant, provided Dietary Reference Intakes (DRIs) for the antioxidant vitamins and minerals, and reviewed the evidence supporting a role for these nutrients in preventing or treating a variety of chronic diseases. A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on normal physiological functions in humans.[1] The DRIs provided by the report include four values: the Recommended Dietary Allowances (RDAs), the dietary intake level that is sufficient to meet the nutritional requirements of most healthy individuals in a particular age and gender group; Adequate Intakes (AIs), which are recommended intakes based on estimated or observed intake levels when data are inadequate to set an RDA; Tolerable Upper Limits (ULs), the highest level of nutrient intake that is likely to pose no adverse health risks for the majority of healthy individuals; and Estimated Average

Intakes (EARs), the intake that is estimated to meet the requirements of half the individuals in an age/gender group.[1] The committee that authored the report found laboratory and epidemiological evidence that diets rich in fruits and vegetables (foods that are high in antioxidants) may be associated with the prevention of certain types of cancer, but found a lack of scientific basis for recommendations regarding any specific nutrient supplement.[2] However, they were unable to establish a direct link between the intake of dietary antioxidants and the prevention of disease, recommending that further, large-scale studies were needed. It has been in the area of prevention of cancer rather than treatment of cancer that much of the discussion and work on antioxidants has focused.

The Origin of Ideas on Diet and Cancer Prevention

The discovery of the vitamins and their requirements in human nutrition was based on findings that the omission of these substances from the diet resulted in the acute appearance of constellations of symptoms. In preventing these symptoms, vitamins function as coenzymes and sometimes as hormones. However, in recent years, as some disease processes have been proposed to be the result of chemical oxidation, several of the vitamins have been found to have an additional set of functions, namely that of preventing such oxidation. The interest in a link between the intake of the antioxidant vitamins and chronic disease prevention is based on this proposed role for the antioxidant vitamins in human nutrition.

It has long been argued that the adequacy of the vitamin supply to cells and tissues influences the development, progress, and outcome of cancers.[3] A major challenge to the integrity and function of cells and tissues is thought to come from chemical species called free radicals (defined as any atom or molecule whose nucleus has one or more unpaired electrons). The body produces these highly reactive species, such as the oxygen radical, as byproducts of some metabolic processes, the process of destroying foreign organisms, and in response to particular types of physical stress. The physiological processes that rid the body of toxins as well as those that metabolize drugs are also believed to lead to free-radical formation.

Free radicals may, in turn, join with other free radicals or react with non-radicals to cause chain reactions and form new radicals. These radicals can then attack cell membranes or their constituent lipoproteins, which is now believed to contribute to atherosclerosis. Free radicals can also attack the DNA, the chemical constituent of genes, causing mutations.[4] The body has evolved antioxidant defenses to protect against free radical–induced damage; for example, cells manufacture repair enzymes that can "destroy free-radical-damaged proteins, remove oxidized fatty acids from membranes, and repair free-radical damage to DNA…"[4] and additional, *extracellular*, antioxidant defenses also exist. Vitamins E and C, the carotenoids, and coenzyme Q10 are potentially involved in these antioxidant defenses. However, these defenses may not be totally effective. Thus, the concentration of free radicals in the body may continue to increase, more damage can occur, and, as a result, the body suffers oxidative stress.[5] Severe oxidative stress may result in cell injury and destruction.

Given what we now know about the potential for free radicals to cause DNA damage and other types of destruction, a theory has developed that one possible cause of diseases such as cancer may be the uncontrolled effect of free radicals. For example, if the DNA damage were not repaired, mutations would result, which theoretically might lead to the development of cancers. If diseases could be caused by free-radical damage, it is also theoretically possible that these diseases could be prevented by increasing the dietary intake of antioxidant-rich foods, foods rich in vitamins E and C and other substances shown to reduce oxidative damage in the laboratory. Yet, as Halliwell[4] notes, while free radicals have been implicated in over 100 human diseases, this implication does not constitute proof of their role in disease formation or proof that treatments aimed at preventing free radicals can prevent or cure disease.

Cancer Development

Research on the association between vitamins and cancer has focused largely on the potential for prevention (although some research focuses on the role of vitamins in cancer treatment). Based on animal studies, carcinogenesis (the development of cancer) has traditionally been viewed as a two-stage process.[6] The first stage, initiation, involves irreversible mutation of genetic sequences, resulting in permanent changes to the genotype (the sequence of DNA carried by every cell). According to this model, this stage is necessary but not sufficient for cancer to develop. The second stage, promotion, involves a change in gene *expression* (the process by which genes are read and the proteins they encode are synthesized, resulting in a "visible" manifestation of the genotype), which requires a promoter substance and thus is believed to be reversible. Promoters enhance the expression of the mutated gene(s) and selectively stimulate the growth of cells that express these genes.

This two-stage model is now considered overly simplistic. Instead, carcinogenesis is now seen as a multistage process[7] however, the two-stage model conceptualizes the belief that cells must undergo a permanent genetic change followed by a stimulus that selectively allows these cells to divide and escape normal growth controls.

The genetic changes necessary for cancer initiation are thought to be caused by the actions of mutagenic chemicals or physical forces (such as high doses of radiation) acting on the DNA, processes that may require metabolic activation. As mentioned above, if the damaged DNA is not repaired quickly, it becomes a stable mutation during the next cycle of DNA replication. Alternatively, miscoding may occur during the repair process.[5] Some mutations that may result in cancer include those that result in the activation of proto-oncogenes and those that inactivate tumor suppressor and other antimetastasis genes.

The next phase, tumor promotion, enhances the probability of additional cumulative genetic damage, including endogenous mutations, by allowing expansion of the population of mutation-containing cells. The likelihood of cancer formation is further increased at this stage by exposure to other mutagenic agents.[6]

The Antioxidant Supplements and Cancer Prevention

Oxidative processes have been implicated in both initiation and promotion of cancer. Likewise, animal studies have revealed effects of the antioxidant nutrients on both processes.

Vitamin E exhibits antioxidant properties by acting as a lipid-soluble free radical scavenger in cell membranes. Thus, vitamin E may be involved in both initiation and promotion stages. Among the other potentially anticarcinogenic effects of vitamin E are its ability to inhibit formation of the carcinogenic chemical nitrosamine from nitrites in some foods, and its ability to promote immune system function.[6]

Vitamin C (ascorbic acid) also acts as an antioxidant, and through its ability to scavenge free radicals, it may have protective effects on biopolymers such as DNA. Like vitamin E, vitamin C may be protective for both initiation and promotion of carcinogenesis. Also, like vitamin E, it is thought to prevent formation of nitrosamine (by converting nitrite to nitrous oxide)[6] and to influence immune system function. Vitamin C has also been reported to affect liver enzymes responsible for detoxification and transformation of carcinogens.[6]

Coenzyme Q10 (also termed ubiquinone and ubidecarenone) is an endogenously synthesized chemical (called a quinone) that is also obtained through food intake. In addition to its role as an electron carrier in the mitochondrial electron transport chain, it can also function as a soluble antioxidant.[8] No recommended daily intake has been established for Q10, no deficiency has ever been shown,[5] and no side effects have been observed at any dose level.[9] In addition to its role as an antioxidant (possibly in conjunction with vitamin E)[10] and as a free radical scavenger, other roles have been proposed for Q10. These include acting as a nonspecific stimulant for the immune system,[9] and playing a role in membrane stabilization, prostaglandin metabolism, inhibition of intracellular phospholipases, and stabilization of calcium-dependent slow channels.[10] Decreased levels of Q10 have been noted with aging and in such disorders as congestive heart failure, cardiomyopathy, cancer, hypertension, Parkinson's disease, spontaneous abortion, male infertility, chronic hemodialysis, and periodontal disease.[10]

As we have briefly reviewed, vitamins C and E and coenzyme Q10 have been implicated in a variety of potential anticarcinogenic processes. This report will review the evidence that supplements of these substances have the ability to prevent some types of cancer.