Unconventional therapies for cancer: 5. Vitamins A, C and E

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Education

Éducation

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*This fifth article continues the series on unconventional therapies for cancer. The purpose and methodology of the review appear in part 1 (*CMAJ *1998;158[7]:897-902). Annotated bibliographies providing more detailed references are available in print from the Canadian Breast Cancer Research Initiative (CBCRI; address appears at end of article). The reference lists and the lay summaries of the findings (published in 1997) can be found on the CBCRI's Web site (***www.breast.cancer.ca***). The following article adapts the lay summary on vitamins A, C and E for clinicians and provides references for the key findings. [Copies of this and other articles in the series can be found on* CMAJ*'s Web site (***www.cma.ca/cmaj/series/therapy.htm***).]*

The potential role of vitamins A, C and E in the prevention of cancer has been the subject of a great deal of research. However, the primary focus of the literature search conducted on behalf of the Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative was to find evidence of the safety and effectiveness of these vitamins taken as supplements in the *treatment* of cancer. Because of the thousands of articles in the scientific and lay literature dealing with these vitamins, it was not feasible to perform an exhaustive review. Instead, a representative sample of articles was collected, especially articles providing information on the effects of vitamin supplements (at standard doses or at megadoses) in clinical studies and review articles with good reference lists.

Canada's Food Guide, prepared by Health Canada, sets guidelines for the recommended daily intake (RDI) of vitamins and minerals. Most people who eat a balanced diet that is made up of a variety of foods and that is rich in fresh fruits and vegetables will meet the RDI for vitamins. However, people who do not eat a balanced diet because of poor health or personal choice may benefit from supplements and are encouraged to discuss this matter with their physician.

There is clear evidence that a diet rich in fresh fruits and vegetables reduces the risk of many diseases, including some types of cancer. The specific factors responsible for this protective effect are not completely understood. However, it seems likely that it is related to complex interactions between constituent phytochemicals that have not yet been completely identified, let alone incorporated into supplements. There is therefore concern that the administration of food extracts or supplements in any form may not confer the benefits of fresh foods.

Despite the concerns of nutritionists and others, many healthy people take daily vitamin supplements, either on their own initiative or on the advice of their physician. Therefore, it is not surprising that many people with cancer consider taking vitamin supplements, particularly since these agents are available at a reasonable price in any pharmacy or health food store. Proponents of supplementary vitamins often recommend combining vitamins A, C, and E and claim that these vitamins improve general well-being, strengthen the immune system and may delay the development and progression of serious disease. The daily doses they recommend may greatly exceed the RDI.

The main proponents of megadose combination vitamin therapy for cancer are the late Dr. Linus Pauling, Dr. Ewan Cameron and, more recently,

The Canadian Breast Cancer Research Initiative does not endorse the use of any particular unconventional therapy. It urges patients to evaluate all evidence carefully and to consult their caregiver in order to make thoughtful and fully informed personal decisions.

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Dr. Abram Hoffer. These proponents base their recommendations for megadose therapy on laboratory studies indicating that these substances, alone or in combination, have positive effects such as immune modulation, tumour suppression and promotion of cell differentiation, which may be beneficial to cancer patients. They have also reported preliminary clinical results suggesting a positive effect.

Vitamin supplements may be manufactured from natural or synthetic sources. For example, vitamin E may be isolated from soybean oil or made from petroleum derivatives. Despite the appeal of "natural" vitamins, research has not found important differences in their effects.

Vitamin A

Vitamin A is one of a group of substances that have similar structures and biological activities and that are known collectively as retinoids. Vitamin A is necessary for normal growth, bone development, vision and reproduction and for the maintenance of the integrity of the skin and mucous membranes. A deficiency in vitamin A, rare in developed countries, can lead to night blindness, dermatoses and decreased resistance to infection. Vitamin A and its major precursor beta-carotene are found in orange fruits and vegetables such as carrots, butternut squash, pumpkins, cantaloupes, mangoes and apricots, and in dark green vegetables such as spinach and broccoli.

Vitamin A and beta-carotene have been proposed as chemoprophylactic agents for cancer in part because epidemiologic studies have shown that the risk of some types of cancer is higher among people with low dietary intakes of foods rich in vitamin A and beta-carotene[1] and among those with low serum levels of vitamin A and beta-carotene.[1–3] However, the relation between the serum levels of other retinoids and cancer risk is not clearly understood. The role of other retinoids has been studied, and the protective effect seems to vary by type of retinoid, cancer and animal species studied.[4]

Because both vitamin A and beta-carotene are fat-soluble vitamins, oral supplements should be taken with food that contains at least a little fat.

Safety

Serious toxic effects from taking vitamin A supplements are relatively rare, but side effects such as headache, irritability, drowsiness, dizziness, itchiness, desquamation and perioral dermatitis may occur. Megadoses may cause liver damage. People with kidney disorders and pregnant women are usually advised to seek medical advice before taking vitamin A supplements.

The recognition of vitamin A's toxic effects seriously limited its clinical value and led to a major effort to identify other, less toxic retinoids that have beneficial effects. As a result, more than 1500 retinoids have been developed and tested, and some are currently being evaluated for their anticancer activity.

Several retinoids are pro-vitamins, transformed into vitamin A in the body. Of these, beta-carotene, which occurs naturally in many foods, has the greatest pro-vitamin activity and is most frequently used by people seeking to increase their intake of vitamin A. It has many advantages over vitamin A: not only is it much less toxic, there are intrinsic mechanisms that limit the amount of beta-carotene transformed into vitamin A, and it has some immunostimulatory effects that seem to be independent of its conversion to vitamin A.

The short-term toxic effects of beta-carotene are minor even at relatively high doses. Temporary hypercarotenemia, especially of the palms of the hands and the soles of the feet, may develop in some people. Of more concern is recent evidence that beta-carotene supplements may increase the risk of lung cancer and lung cancer recurrence among people who smoke.[5]

Laboratory and clinical evidence

Much of the evidence regarding the potential effectiveness of vitamin A and beta-carotene had to be deduced from articles evaluating the effect of retinoids and carotenoids as a class of compounds. Some animal studies have shown the ability of vitamin A, beta-carotene and other retinoids to enhance the immune response, to retard tumour growth and to decrease the size of established tumours. For example, beta-carotene has been shown to increase the production and tumoricidal activity of human monocytes, lymphocytes and macrophages.[6–9] Other studies have demonstrated that retinoids, particularly in combination with inferons, inhibit the proliferation of malignant cells.[10,11] More recently, a preclinical study has indicated that fenretinide, an analogue of vitamin A, may be useful in the prevention and treatment of breast cancer. The agent demonstrated cytostatic activity against human mammary cancer cell lines, and in rat studies it has inhibited mammary gland development, suppressed carcinogen-induced mammary cancer and caused regression of invasive mammary cancer. The investigator also noted a possible synergism between fenretinide and tamoxifen and stated that clinical studies of the combination were planned.[12]

The anticancer effects of retinoids are thought to be due to inhibition of cell proliferation and promotion of cell differentiation.[2,3,13,14] Recently, progress has been made in establishing a possible mechanism of action at the cellular level. For example, the presence of retinoid receptors

has been reported, and one study using breast cancer cells showed that retinoids attaching to these receptors influenced gene expression and cell proliferation.[11] The ability of some retinoids to induce cell differentiation in acute promyelocytic leukemia has been confirmed in clinical studies.[15] In animal studies, these effects have been found to be greater and to last longer if the retinoids are given in combination with other agents such as interferon or conventional chemotherapeutic agents.[16,17]

In one clinical study, plasma retinol levels were found to be lower in cancer patients than in control subjects; among cancer patients, the retinol levels were higher in those who subsequently responded favourably to chemotherapy. Serum levels were increased by daily retinol supplementation, but it is unclear whether this resulted in any therapeutic benefit.[18] Another study found that 13-*cis*-retinoic acid (13-cRA) — a vitamin A analogue — in combination with interferon-α had beneficial effects in patients with cervical cancer.[19] Other retinoids have been shown to be effective in retarding the proliferation of cutaneous tumours, especially in combination with interferon.[20]

Results of a study in which high doses of vitamin A were given to patients with lung cancer were negative,[21] and a recently reported large study involving smokers receiving beta-carotene and vitamin A reported the unexpected finding of an increased risk of lung cancer.[5] As a result, researchers are proceeding more cautiously with studies examining the potential role of vitamin A and beta-carotene in the prevention and treatment of cancer.

Vitamin C

Unlike many other animals, humans cannot manufacture vitamin C and must therefore obtain it from dietary sources. A water-soluble vitamin, it is found in many fruits such as oranges, grapefruit, strawberries, raspberries and kiwi fruit, and in vegetables such as cabbage, tomatoes and bell peppers.

Vitamin C is known to play an important role in the synthesis of collagen,[22] to promote wound healing and to influence many immunological and biochemical reactions in the body. It is also considered to be one of the most potent and least toxic antioxidants for humans.[22] More recently, studies have suggested that vitamin C may protect the integrity of cell membranes and promote cell differentiation.[23]

Vitamin C deficiency, which results in scurvy, is rare in people who are able to eat a well-balanced diet. However, it is widely held that the body's requirement for ascorbic acid increases during periods of physical or chemical stress and in elderly people. This belief has led to the widespread use of vitamin C supplements.

There is some epidemiologic evidence that populations whose dietary intake of vitamin C is high have a decreased risk of some types of cancer.[24] This may be due to the antioxidant function of the vitamin or its ability to block the formation of *N*-nitrosamines, which are formed in the stomach following the ingestion of certain foods.[22] The strongest epidemiologic finding has been the association between high intakes of foods rich in vitamin C and a reduced risk of stomach cancer.[22] There is weaker evidence that high levels of vitamin C are associated with a decreased risk of cervical cancer in smokers.[24] Some other studies suggest that vitamin C may be protective against cardiovascular disease and cataracts.[25]

Pauling, Cameron and Hoffer, the main proponents of megadose vitamin therapy for cancer, and some other scientists consider that the daily intake of vitamin C should be much higher than the current RDI of 60 mg/d, which is designed to protect against scurvy.[26–30] However, they recognize that more research is needed to determine the appropriate dose. Megadose vitamin C therapy for cancer may be administered either intravenously or orally,[27,31] and proponents advise that it can be given concurrently with chemotherapy.[32] They claim that megadose vitamin C therapy (alone or in combination with megadoses of other vitamins and nutrients) improves the well-being and quality of life of cancer patients and that it may result in improved survival. One protocol for its use was provided by proponent in 1991.[33]

Safety

Vitamin C supplements are generally well tolerated. However, high doses may cause stomach irritation, heartburn, nausea, vomiting, drowsiness, headaches and rash. High doses may also acidify the urine, alter the results of urine tests, affect iron metabolism and possibly increase the risk of oxalate deposits in the kidney or bladder.[25,34]

Vitamin C may interfere with the absorption or activity of a number of agents, including anticoagulants, iron, vitamin B_{12} and vitamin E. Effects of vitamin C on the absorption or excretion of chemotherapeutic drugs are possible, but reports of such effects were not found. High doses of vitamin C during pregnancy may cause subsequent vitamin C deficiency in newborns.[22,25]

In adults, there is significant anecdotal evidence that vitamin C is safe at a dose of 1 g/d, and very minimal toxic effects have been reported even at much higher doses.[35] However, formal, well-designed studies of the short- and long-term toxic effects of vitamin C were not found.

Proponents caution that sudden withdrawal of supplementary vitamin C may be harmful, but no studies documenting this effect were found.

Laboratory and clinical evidence

Several reviews describe the antioxidant and general immunostimulant properties of vitamin C.[28,29,36] In laboratory experiments, vitamin C has been shown to have a range of effects that could be beneficial to cancer patients, including tumour regression, the inhibition of tumour growth and increased survival of animals with implanted tumours[35,37] as well as promotion of cell differentiation and stabilization of gene transcription.[23]

Results of some studies also suggest that ascorbic acid may have a direct cytotoxic effect on tumour cells[36,38,39] and that it may decrease the toxicity and enhance the cytotoxic effect of some chemotherapeutic drugs.[36,39–41] For example, in one animal study high doses of vitamin C were associated with reduced toxic effects of adriamycin on heart muscle.[41] Some studies suggest that malignant cells are more sensitive than normal cells to the cytotoxic effects of ascorbic acid.[37,38] However, it is unclear whether these cytotoxic effects occur at the concentrations of ascorbic acid achievable by oral or even intravenous administration of vitamin C supplements in humans.

Some preliminary clinical data indicate that vitamin C may improve the survival of cancer patients. However, most of the studies were either anecdotal reports[42,43] or uncontrolled case series,[26,32] and therefore the results, although suggestive, are not conclusive.[44] The study designs and the techniques used in the statistical analyses of the findings have been superseded and are no longer regarded as sufficiently rigorous to guide clinical treatment planning. In 1979 and 1985, 2 randomized controlled trials of vitamin C therapy in patients with advanced cancer reported negative results.[45,46] Proponents criticized the design of both these studies, specifically the focus on patients with advanced disease and limited life expectancy, the route of administration (oral rather than intravenous), the sudden withdrawal of vitamin C in some cases and patient selection criteria. Others claimed the trials were definitive.[47] No randomized controlled trials of the effects of vitamin C on the progress of early or less advanced cancer were found.

Vitamin E

Vitamin E is a fat-soluble vitamin that exists in a variety of forms in many foods. It is found in spinach, nuts, sunflower seeds, olives, asparagus, vegetable oils, mangoes, wheat germ and whole-wheat breads. Its most common form in a Western diet is α-tocopherol. Only 20% to 60% of vitamin E is absorbed from dietary sources, and as the dose increases (e.g., in megadose therapy) the fraction of vitamin E absorbed decreases. Nonetheless, vitamin E deficiency is rare in adults.

Descriptive studies have shown that low serum levels of vitamin E are associated with a slightly increased risk of cancer in some populations, but data are limited and somewhat inconsistent.[48] Daily supplements of α-tocopherol have been shown to increase the serum level, but the effect of this increase on the risk of cancer is unknown.

Like vitamins A and C, vitamin E is considered to have antioxidant properties and immunostimulatory effects. Vitamin E supplements have been used in the management of a number of conditions, including malabsorption disorders, cardiovascular disease, precancerous conditions of the mouth and cancer.[49]

The mechanisms of action of vitamin E are poorly understood. However, its potential role in the prevention and treatment of cancer may be related to its lipid antioxidant properties,[48] its ability to inhibit carcinogenic effects of some chemicals[48,50] and its immunostimulatory properties.[51,52]

Proponents also believe that megadoses of vitamin E can have a beneficial effect on cardiovascular diseases.

Safety

The toxicity of vitamin E in adults appears to be low. Clinical trials have shown that large doses (e.g., 200–800 mg/d) do not result in serious side effects in most adults,[53] with the possible exception of individuals taking oral anticoagulant therapy and those with vitamin K-related clotting disorders. High levels of vitamin E can adversely affect the absorption of vitamins A and K, and long-term use of high doses may cause nausea, diarrhea and blurred vision. High-dose therapy in infants may be associated with more serious side effects.[34,49]

Laboratory and clinical evidence

Although there has been some research into vitamin E's role in cancer prevention, very little research was found that addressed its potential role in cancer treatment.

One laboratory study using human breast cancer cell lines demonstrated that vitamin E inhibited cell proliferation.[54] No in vivo or clinical studies confirming this effect were found. Another laboratory study showed that vitamin E inhibited the synthesis of prostaglandins, an effect that may have an impact on immunocompetence.[55]

A clinical study revealed a positive response to vitamin E therapy in patients with oral leukoplakia,[53] but no clinical studies were found that reported on the effect of vitamin E alone on the progress of cancer. A study involving patients with benign breast disease showed that vitamin E supplements were not beneficial.[56]

Combination vitamin therapy

The proponents of megadose vitamin therapy for cancer usually recommend combinations of vitamins A (or beta-carotene), C and E and often recommend including other agents such as selenium. They believe that this combination therapy is likely to have beneficial synergistic effects. There are several protocols for combination therapy, one of which is the Hoffer regimen.[57]

Several studies were found that reported the effects of combination vitamin therapy in patients with cancer, usually advanced cancer, and these provide some evidence of increased benefits.[55,57–60] However, methodologic weaknesses detract from the studies' findings. Proponents note that only some patients are "good responders," but no method of identifying these individuals before initiating therapy has been developed.

Conclusion

There is some laboratory evidence and some clinical evidence that vitamins A, C and E, given separately or in combination, may have value in the management of cancer. However, there is a lack of solid scientific evidence of the sort required to support a recommendation that cancer patients take vitamin supplements. Furthermore, the different preparations available of these vitamins may have different effects, and there may be significant interactions (both positive and negative) between them. In addition, vitamin supplements may interact with other drugs or treatments being used; none of these interactions is well understood.[61]

Vitamin supplements are readily available, can usually be self-administered and are relatively inexpensive and nontoxic for most adults. As a result, many cancer patients take them. Patients should be encouraged to discuss the use of vitamin supplements, and any other unconventional therapies they are currently using or contemplating, with their physician in order to monitor their effects and avoid undesirable interactions as much as possible.

Further laboratory research is needed to improve our understanding of the functions of vitamins A, C and E and to establish their potential role in the treatment of cancer. There is also a need for well-designed clinical studies to examine the transferability of any positive laboratory findings to cancer patients. The value of vitamin A, C and E supplements, used separately or in combination, in the prevention and treatment of cancer will only be established as additional scientific studies are conducted of their effectiveness and their appropriate clinical indications and doses. The complexity of the research required in this area should not be underestimated. In studies of the protective or therapeutic effects of vitamin supplements, it is usually very difficult to determine whether any observed benefits are due to the supplements, dietary changes or other factors.

This article reports some of the work carried out by the Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative (CBCRI). The CBCRI is the main funder of breast cancer research in Canada and was established in 1993 as a consortium of the Canadian Cancer Society (CCS), the National Cancer Institute of Canada (NCIC) — which also serves as the administrative home of the CBCRI — and the federal government (through the participation of the Medical Research Council of Canada and the National Health Research and Development Programme). In addition to the author, a number of other CBCRI staff worked on the project, including Dr. Carmen Tamayo (research associate), Ms. Rebecca McDonald and Ms. Jess Merber. Others contributed to the reviews of specific agents. The task force was chaired by Ms. Donna Cappon. Dr. Kaegi was the Director of Medical Affairs and Cancer Control for the CCS and the NCIC and staff partner with the task force.

714-X will be the topic of the final article in the series, to appear in the June 16 issue.

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Alternative Therapies in Health and Medicine
The Journal of Alternative and Complementary Medicine

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