

# LifeExtension

## Cancer: Should Patients Take Dietary Supplements?

There continues to be controversy as to whether cancer patients should take certain vitamin and mineral supplements. Some in mainstream medicine have attacked the use of vitamin supplements as being potentially harmful, despite published scientific evidence indicating that cancer patients who supplement benefit. The criticism about cancer patients taking supplements is not limited to conventional oncologists. There have also been debates among Life Extension advisors as to what supplements are best for cancer patients to take.

Unlike heart disease, cancer is a very complicated disorder. No one has definitively shown what supplements a cancer patient should take nor at what stage in the disease process the supplements should be initiated. It could be that some dietary supplements are of benefit at some phases of cancer treatment (such as enhancing immune function), but detrimental in others (such as protecting cancer cells against the effects of certain chemotherapy drugs).

Most people familiar with published scientific literature are surprised that there is any argument over the value of dietary supplements and cancer treatment. The problem is the complexity of cancer compared to other diseases. For instance, there is a scientific consensus that folic acid is beneficial in cardiovascular disease patients because it lowers homocysteine and protects the arterial system via other mechanisms; no one argues against this. There is also substantial evidence that folic acid dramatically lowers the risk of many forms of cancer; few scientists disagree with this premise either. However, the role of high-dose folic acid in the treatment of cancer is not as clear-cut. Every human and animal cancer study indicates that folic acid improves survival, yet those familiar with the molecular actions of folic acid are concerned that very high amounts could potentially facilitate cancer cell propagation.

In the following section, we review all studies involving the use of dietary supplements by human cancer patients. We also discuss reasons why some scientists believe that cancer patients should approach supplementation with a degree of caution.

The reader should know that no organization has ever methodically analyzed the scientific literature to address the complex issue of using dietary supplements in the treatment of cancer. Although articles have been written about isolated effects of certain nutrients, there has not been an attempt to consolidate this knowledge in a way that provides practical guidance for the cancer patient.

### **Human Research on Cancer and Dietary Supplements**

Although there are hundreds of published studies showing that the ingestion of certain nutrients may reduce cancer risk, relatively few investigate the effects of dietary supplement intake by those already stricken with cancer. This paucity of data has enabled mainstream oncologists to speculate that certain dietary supplements might protect cancer cells from apoptosis

(programmed cell death). The assertion made by some oncologists is that there may be a risk when cancer patients take certain dietary supplements.

To get the bottom-line facts on what happens to cancer patients who take dietary supplements, a MEDLINE search was conducted using key words to access all peer-reviewed published studies relating to groups of cancer patients who used various dietary supplements. The criteria for the studies selected was that the dietary supplement had to show an effect on the clinical outcome of the patient--preferably relating to long-term survival--as opposed to therapies that offer a short-term benefit, such as mitigating chemotherapy toxicity. Oncologists generally acknowledge that supplements can mitigate chemotherapy and radiation therapy side effects. The question is whether cancer patients taking supplements are actually surviving longer. Below is a synopsis of the MEDLINE findings:

1. A study was conducted on non-small cell lung cancer patients over age 60 that had already had the primary tumor(s) surgically removed. The prognosis for this type of cancer is grim. The doctors compared vitamin users to nonusers and measured blood folate as an indicator of folic acid intake. The median survival for the nonusers was only 11 months compared to an astounding 41 months for the vitamin users. Supplement users, in other words, survived almost four times longer than nonusers. In those patients with higher blood levels of folate, there was a 68% improvement in survival. Because the doctors adjusted for other mortality factors, the findings of this study suggest that cancer patients should take vitamin supplements (Jatoi et al. 1998).
2. A more specific study looked at a group of transitional cell bladder cancer patients. One group was given BCG (tuberculosis vaccine) immune-augmentation therapy plus the recommended daily allowance (RDA) of vitamins. The second BCG-treated group received the RDA plus 40,000 IU of vitamin A, 2000 mg of vitamin C, 400 IU of vitamin E, 100 mg of vitamin B6, and 90 mg of zinc. After 5 years, the tumor recurrence rates were 91% in the group receiving the low-potency RDA vitamins, but only 41% in the mega dose vitamin group. In this study, large doses of vitamins resulted in a 55% reduction in tumor recurrence (Lamm et al. 1994).
3. Malignant melanoma is virtually impossible to stop once it has spread beyond the primary lesion. A rare form of melanoma occurs in the iris of the eye, and it is considered high risk because it is often found too late. Nine random high-risk patients with T3 melanoma of the eye first underwent standard conventional therapy to eradicate the primary tumor. These patients were then put on a supplement regimen consisting of folic acid, trace minerals, amino acids, and fatty acids. After 80 months of follow-up, none of these nine patients experienced recurrent disease, which was significantly better than a similar group of high-risk melanoma patients who did not receive these supplements. (The control patients consisted of similar adjusted T3 cases selected from the Swedish official registries and T2 patients from Germany.) Because 100% of these high-risk patients were free of disease after almost 7 years, this provides further piece of evidence of the potential value of dietary supplementation in the cancer patient (Tallberg et al.

2000).

4. Breast cancer patients commonly undergo chemotherapy to reduce the risk of future metastasis. Despite the severe toxicity of chemotherapy, many women experience aggressive metastatic disease and die. Once metastatic disease manifests, the 5-year survival rate is only 15%. A review was conducted of various chemotherapy regimens in order to ascertain the percentages of objective remissions in metastatic breast cancer patients. Of the drugs tested, 5-fluorouracil (5-FU) came in last, but when folic acid was added, objective remissions increased significantly (Kreienberg 1998).
5. The drug 5-fluorouracil (5-FU) is commonly used in visceral cancers (such as colon, liver, pancreatic), but has not shown a high degree of efficacy. A randomized trial of patients with metastatic colorectal carcinoma compared the effects of 5-FU administered alone and in combination with folic acid. Both groups were comparable in respect to age, sex, and numbers of metastases. Compared to the group receiving 5-FU by itself, the patient group receiving the 5-FU plus folic acid experienced a 40% arrest of tumor growth and a 76% overall reduction in tumor progression indicating a 47% difference between the 5-FU and folate group and the 5-FU group. Survival time in the group receiving the 5-FU plus folic acid was 47% greater than the group receiving the 5-FU by itself. The addition of folic acid to this chemotherapy drug regimen resulted in an improvement in the therapeutic profile and a significant prolongation of the survival time (Loffler et al. 1992).

	<b>5-FU</b>	<b>Folic acid and 5-FU Difference</b>	
<b><i>Complete or partial remission</i></b>	9%	versus 16%	7%
<b><i>Arrest of tumor growth</i></b>	20%	versus 60%	40%
<b><i>Progression</i></b>	71%	versus 24%	47%
<b><i>Total</i></b>	100% of patients in group	100% of patients in group	

- 6.
7. Advanced cancer patients exhibit multifaceted defects in their immune capacity that are likely to contribute to an increased susceptibility to infections and disease progression. This immune impairment also constitutes a barrier to effective immunotherapeutic interventions. A chronic inflammatory condition associated with increased oxidative stress has been suggested as one of the responsible mechanisms behind the tumor-induced immune suppression. A study was conducted on 12 advanced colorectal cancer patients to ascertain if supplementation with the antioxidant vitamin E could enhance

immune functions. These colorectal cancer (Dukes's C and D) patients received a daily dose of 750 mg of vitamin E beginning 2 weeks prior to intervention with chemotherapy or radiation treatment. The results showed that short-term supplementation with vitamin E led to increased CD4:CD8 ratios and enhanced capacity of their T-cells to produce the T helper 1 cytokines, interleukin 2, and IFN-gamma (Malmberg et al. 2002).

There are other human studies showing a benefit when cancer patients take dietary supplements. We could find no studies on MEDLINE indicating a detrimental effect. The findings from animal studies (reported on next) support the positive human findings that show that dietary supplements appear to enhance survival.

### **Animal Research on Cancer and Dietary Supplements**

To obtain additional information about what happens when an organism afflicted with cancer is administered dietary supplements, we extended our MEDLINE search to *in vivo* animal studies. As was done with the human study search, keywords were aimed at accessing all peer-reviewed published studies relating to the effects of dietary supplements on animals with different forms of cancer. The criteria for studies selected were that the dietary supplements had to show an effect on survival. Below is a synopsis of the MEDLINE findings:

1. A debate among medical oncologists relates to the combined use of certain dietary supplements and chemotherapy. A study on rat mammary tumors provided some interesting data but also revealed part of the controversy. In this study, rats were administered one of three chemotherapy drugs (5-FU, doxorubicin, or cyclophosphamide) and then provided with a wide dosage range of folic acid. In the folic acid-deficient group, tumor growth was impeded. However, when higher amounts of folic acid were administered, even greater tumor growth-inhibiting effects were observed. When looking at the data, low folate inhibited tumor growth by an average of 41%, moderate folic acid supplementation inhibited tumor growth by an average of 67%, and very high folic acid administration resulted in an average of 75% in tumor inhibition. Folic acid supplementation doubled the efficacy of one of the drugs (cyclophosphamide) and improved survival in the 5-FU treated animals (Branda et al. 1998).
2. In a group of mice with ascites sarcoma, a four- to six-fold surplus of folic acid in oral application reduced the toxicity of the chemotherapy drug methotrexate. Moreover, adding these high amounts of folic acid into their drinking water prolonged the survival of these mice (Motycka et al. 1975).
3. In a group of mice bearing leukemias and solid tumors, a combination of oxidized vitamin C and vitamin B12 inhibited division of the cancer cells. The mice were injected with the vitamins and after 19 days, all of the controls had died, whereas more than 50% of the mice were alive after 60 days in the vitamin-treated group. This study demonstrated that when B12 is combined with vitamin C, the cobalt nucleus of B12 attaches to vitamin C, forming cobalt ascorbate. Additional tests proved that cobalt ascorbate plus vitamin C inhibited tumor cells (Poydock 1991).

4. The effects of methylcobalamin (vitamin B12) were examined in mice with liver, lung, and Ehrlich ascites tumor cells. The growths of tumors in some groups of the mice were suppressed by the 7-day administration and their survival was longer than that of untreated mice (Shimizu et al. 1987). In a contradictory animal study, the effect of methylcobalamin and vitamin B12 reduced the survival of rats with liver cancer. This is the only study where vitamins actually inhibited survival (Kal'nev et al. 1977).
5. Cancer spreading (metastasizing) throughout the body often culminates in death. Immune suppression is one mechanism that cancer cells use to establish colonies (metastatic lesions). Scientists investigated the effects of an antioxidant called astaxanthin in stress-induced, immune suppressed mice. When exposed to stress, the number of natural killer cells (NK) and other immune cells was reduced and an increase in liver lipid peroxidation was observed. After 4 days of astaxanthin administration, immune dysfunction induced by stress improved. In this same study, cancer cells were injected into mice and the effects of tumor development and metastatic lesions were evaluated in response to induced stress. Daily administration of astaxanthin for 14 days markedly attenuated the promotion of hepatic metastasis induced by stress. The results of this study suggest that the antioxidant, astaxanthin, improves antitumor immune response by inhibiting lipid peroxidation induced by stress (Kurihara et al. 2002).

Despite these studies indicating that supplements confer a significant anticancer benefit, there are certain supplements that cancer patients might consider avoiding, at least during active treatment. These issues are addressed in the next section and in the protocols entitled *Cancer Chemotherapy* and *Cancer Radiation Therapy* that appear in this book.

### **Do Antioxidants (Concurrent with Conventional Therapy) Bolster or Diminish Survival Odds?**

Abram Hoffer, M.D., Ph.D., contends that the concept of antioxidants decreasing the efficacy of chemotherapy is conveyed more and more by orthodox oncologists. It is, in fact, speculated that the number of oncologists opposed to patients taking antioxidants while receiving chemotherapy may be as high as 75%.

Although antioxidant therapy is a hotly debated issue, the benefits derived from chemotherapy are equally so. Even within the field of standard oncology, there is debate as to the merit of chemotherapy except for in a small number of cancers (Moss 1995).

Before one can claim that antioxidants should be withheld, credible evidence should be presented showing that chemotherapy has merit. At the Comprehensive Cancer Care 2001 Conference, it was reported that 31% of cancer patients abandon chemotherapy before completion due to intolerable psychological and physical stresses.

Amifostine, a synthetic variant of the amino acid cysteine, is prescribed to reduce radiation toxicity. Amifostine reduces toxicity of treatment without depreciating the anti-cancer effects (Mehta 1998). There is no evidence of defusing the effects of radiotherapy with Amifostine (Perez et al. 1998). Cardiozane (ICRF187), an antioxidant with 500 papers showing its relative

safety, is prescribed to counter Adriamycin toxicity (Alderton et al. 1992). Mesna, another synthetic antioxidant, makes possible the use of the anticancer drug Ifosfamide, which (otherwise) damages the urinary system (Brock et al. 1979). Synthetic antioxidants, though somewhat toxic in nature, do not generate controversy because they are physician-prescribed and not patient-managed. It appears only orthomolecular or natural antioxidants are potentially dangerous, according to mainstream oncologists.

Most natural antioxidants, including vitamin C, are under ongoing scrutiny and often attack. The charges that vitamin C impairs the effects of chemotherapy appear to have kindled from an interview conducted with Larry Norton, a chemotherapist with a focus on breast disease at Memorial Sloan Kettering. An account of the interview that ran on the front page of newspapers (in 1997) charged that Sloan Kettering researchers had found that vitamin C blunted the effects of chemotherapy in breast cancer cells.

Dr. Charles Simone, a respected voice in natural medicine, clarified the media hype by saying that researchers had simply determined that tumor cells (injected with vitamin C) take up larger amounts of the nutrient than noncancerous cells (Agus et al. 1999). The story that was ultimately reported had a different slant, that is, because tumor cells are vitamin C responsive, ascorbic acid stymies the effects of chemotherapy by neutralizing free radicals, molecules produced by various chemotherapeutic drugs to kill the cancer. Dr. Simone cautions that jumping from a fact (cancerous cells take up more vitamin C) to a factoid (vitamin C interferes with chemotherapy/radiation therapy) is an unfortunate leap that may have impeded progress for many cancer patients.

Dr. Simone cited more than 350 studies, involving 2000 cancer patients that showed that antioxidants extended the life span of cancer patients and improved quality of life. One such study involved 50 early stage breast cancer patients, some of whom were relegated to radiation therapy and others to a combination of radiation and chemotherapy. All participants (in union with conventional therapies) took large doses of nutrients. More than 90% of both groups noted improvement in their physical symptoms, cognitive ability, sexual function, general well-being, and life satisfaction. Not one subject in either group reported a worsening of symptoms (Simone et al. 2000).

Dr. Simone explains the pathways through which antioxidants work to restrain cancer:

- Antioxidants inhibit protein kinase C, restraining tumor cell division and proliferation.
- Antioxidants inhibit oncogene expression, genes that give rise to tumors.
- Antioxidants promote differentiation by altering growth factors. Undifferentiated cells depart (in appearance) from the highly recognizable (differentiated) cells of the tissue of origin. For example, healthy cells have a typical appearance microscopically: A healthy liver cell cannot be mistaken for a colon cell; or a colon cell cannot be mistaken for a kidney cell. The greater the departure from the unique character of the cell (a lack of differentiation) the greater the level of malignancy.

- Antioxidants block destruction imposed by free radicals, protecting vital tissue from damage.

Dr. Hoffer adds that he has treated more than 1100 cancer patients with high doses of vitamin C (most of whom were concurrently receiving chemotherapy) (Hoffer et al. 1993a; Hoffer et al. 1993b; Hoffer 1994; Hoffer 1996). Upon examining health histories, Hoffer found that the mean difference in prolongation of life was heavily in favor of the use of vitamins. In the first Hoffer/Pauling series published, patients on the Hoffer program lived 10-20 times longer than patients not receiving vitamin C.

Various vital functions dependent on healthy antioxidant systems are challenged during cancer. Collapse of internal defenses (either partial or total) occurs through nutrient depletion as observed among cachexic patients, that is, those individuals evidencing a profound state of general ill health and malnutrition, marked by weakness and emaciation. (About 40% of cancer patients die due to malnutrition.) Also, naturally occurring antioxidants and enzymes are often severely exhausted among cancer patients undergoing aggressive therapies, leaving the patient defenseless in regard to free-radical attack. Adjunctive antioxidant therapy is not adding something foreign to the body but rather replacing natural substances withdrawn as a result of treatment.

A valuable contribution to the quandary of whether to use antioxidants with chemotherapy or radiation is available to physicians and patients at <http://www.thorne.com/altmedrev/.fulltext/5/2/152.html>.

Drs. Davis Lamson and Matthew Brignall have abridged a lengthy dissertation into accessible reference guides, showing antioxidant interactions (both positive and negative) when coupled with traditional therapies, for example, popular antioxidants (vitamins A, C, E, beta-carotene, and melatonin) interlaced positively with radiotherapy, enhancing the therapeutic intent (Lamson et al. 2000).

Exceptions to the reference guides routinely surface, but Lamson et al. (1999) declare that (to date) only three agents, classified as antioxidants, have been shown to decrease the effectiveness of radiation or chemotherapy *in vivo* :

- N-acetyl-cysteine (NAC) reduced the therapeutic effect of anthracycline-type chemotherapy agents (doxorubicin and bleomycin), which kill cells by generating oxygen radicals. Alkylating agents (such as cisplatin) and hormonal therapies were not affected.
- Beta-carotene decreased the effectiveness of antimetabolites (5-FU and methotrexate). Conversely, beta-carotene increased the efficacy of radiotherapy, as well as alkylating, anthracycline, and platinum chemotherapy agents.
- Tangeretin (a flavonoid found in citrus fruit) reduced the chemotherapeutic effect of platinum compounds such as cisplatin and carboplatin. Tangeretin interfered with tamoxifen, a nonsteroidal antiestrogen used to treat estrogen-dependent cancers

(Bracke et al. 1999).

Dietary curcumin inhibited chemotherapy-induced apoptosis through inhibition of reactive oxygen species. A 70% reduction in chemotherapy-induced apoptosis in MCF-7, MDA-MB-231, and BT-474 human breast cancer cells was noted. Supplemental curcumin as well as curcumin-containing foods were proposed as being possible antagonists to conventional treatment. However, additional studies are needed to determine whether breast cancer patients, undergoing chemotherapy, should avoid curcumin supplementation (Somasundaram et al. 2002).

Dan Labriola, M.D., and Robert Livingston, M.D., suggest a plan for adjunctive antioxidant therapy aimed at avoiding possible undesirable interactions with conventional treatments. They acknowledge that a number of chemotherapeutic agents are dependent upon reactive oxygen species for performance. Drs. Labriola and Livingston refer to the period when conventional treatments do their work as the protected zone. They contend that the protected zone can last for varying amounts of time, depending on the drug, the procedure and dosage, other drugs or treatments in the regime, and the patient's overall health.

Pinpointing the protected zone and protecting this interval (a process that requires the expertise and clinical judgment of a physician and an oncology pharmacist) allows time for the cytotoxic agent to enact its kill. The clinical objective is to avoid high antioxidant levels while the drugs are still active and vulnerable to interference (Labriola et al. 1999). Labriola, although criticized by some for astringency, advises looking at the long-term prognosis, not the short-term "feel good" response, obtained from antioxidants while undergoing aggressive therapies.

Jeff Bland, Ph.D., scientist and educator, reported at the Comprehensive Cancer Care 2001 Conference that leaders in the field endorse pulse therapy as the appropriate means of administering nutritional support concurrent with toxic treatment. Reentering with supplementation 2-3 days after the large chemotherapeutic bolus allows time for a massive cancer kill followed by a period of rebuilding (Bland 1999; 2001). If conventional treatment is the patient's election, this dosing pattern appears to allow the body the full effects of conventional treatment, plus the benefit of an antioxidant program a few days later. Juices, rich in antioxidants, may (according to Dr. Bland) also merit caution during the few days of the protected zone.

Dr. Keith Block, director of the Block Medical Center and the Institute for Integrated Cancer Care, although in favor of antioxidant therapy, admits the ultimate answer is not available. The downside to the equation is that individuals with cancer are not able to wait for proof. The general theme of Comprehensive Cancer Care 2001 (presenting the best of worldwide research) was that it appears unreasonable and heartless to totally withhold materials that (to date) show survival enhancement. Dr. Block concluded: "I would not (personally) take chemotherapy if antioxidants were not also on board" (Block 2001). Dr. Block believes that factoring in circadian rhythms regarding chemotherapeutic administration influences toxicity and anticancer activity and best serves the patient's welfare. Dr. Block has a highly esteemed

practice in Evanston, Illinois, (847) 492-3040.

An opposing view (regarding antioxidant therapy) comes from Dr. Rudolph Salganik, a Russian scientist currently at the University of North Carolina. Dr. Salganik states that free radicals, generated through chemicals and radiation, should be allowed to work unencumbered, that is, without interference from antioxidants. According to Dr. Salganik, apoptosis or regulated cell death eliminates unwanted and damaged cells, including those precancerous and cancerous. He continued, "Since reactive oxygen species (ROS) act as essential apoptotic mediators, we [our team] reasoned that increasing ROS levels might enhance apoptosis and thereby slow tumor growth." A brain tumor was used as the model to test the impact of an antioxidant-depleted diet, that is, a diet capable of increasing ROS levels compared to an antioxidant-enriched diet on tumor growth.

The antioxidant-depleted diet dramatically increased apoptosis in mouse tumor cells but did not affect normal tissue. Salganik says that the presence of increased oxidant stress within tumors indicates that the likely mechanism of apoptosis is via ROS and DNA oxidative impairment. As reactive oxygen species promoted apoptosis, tumor growth was inhibited; in contrast, the antioxidant-rich diet had no impact on the growth of the tumor. The Salganik team concluded that when the multitudes of oxidants are not suppressed by antioxidants, they mediate apoptosis, or cell death, the exact intent of cytotoxic therapies (Salganik et al. 2000).

Dr. Salganik later reported that intake of exogenous antioxidants (vitamins E, C, and beta-carotene) could protect against cancer and other degenerative processes in individuals with innate or acquired high levels of reactive oxygen species (ROS). Screening populations (for high or low levels of ROS) could provide a scientifically grounded application for antioxidant supplementation, a program that could vastly contribute to the nation's overall health (Salganik 2001).

Positive Results of High Dose Antioxidant Therapy During Chemotherapy and Radiation Studies have demonstrated that antioxidant vitamins can enhance the efficacy of certain chemotherapeutic agents on tumor cells in culture (Prasad et al. 1994; Prasad 2003). Antioxidant vitamins could be an important adjuvant to standard treatment of human cancers (Prasad et al. 1999).

An *in vitro* study was undertaken to ascertain if antioxidant vitamins could enhance the cytotoxic and apoptotic effects of paclitaxel and carboplatin on non-small cell lung cancer ( Pathak et al. 2002).

The human non-small cell lung cancer cell line H-520 was treated with a mixture of the antioxidant vitamins C, E, and beta-carotene and paclitaxel and carboplatin, both individually and in combination of various doses in different sequences. The mixture of antioxidant vitamins by itself led to 15% apoptosis. Simultaneous treatment of paclitaxel and carboplatin produced 40% apoptosis, while paclitaxel treatment 24 hours prior to carboplatin treatment caused 54% apoptosis. However, the most significant improvements in the degree of apoptosis were observed when cells were pretreated with an antioxidant vitamin mixture immediately before

treatment with paclitaxel and carboplatin (70% apoptosis) or pretreated with the antioxidant vitamin mixture 24 hours prior to treatment with paclitaxel, which was then followed 24 hours later by treatment with carboplatin (89% apoptosis).

The apoptotic effects of paclitaxel and carboplatin are enhanced by antioxidant vitamin pretreatment. Further, the most promising sequence of agents that emerged in this study was the pretreatment with the antioxidant vitamin mixture 24 hours prior to treatment with paclitaxel, which was then followed 24 hours later by treatment with carboplatin.

Another clinical trial was conducted to examine the outcome of treatment with paclitaxel and carboplatin alone and in combination with an antioxidant vitamin mixture of 60 mg a day of beta-carotene, 1025 mg a day of alpha-tocopherol, and 6100 mg a day of ascorbic acid on 65 cancer patients with squamous cell carcinomas (n = 37), adenocarcinomas (n = 16), large cell carcinomas (n = 6), and poorly differentiated carcinoma (n = 6). The outcome was very encouraging with overall survival at 33% after 1 year with the treatment of paclitaxel and carboplatin alone, and 54% when patients were treated with paclitaxel and carboplatin combined with the antioxidant vitamin mixture. Although the study was limited due to the small number of patients, the research confirms a need for further clinical trials to examine the role of vitamins in the treatment and management of cancer (Unpublished 2002).

### **The Molecular Effects of Folic Acid**

Few people have ever heard the word methylation, yet this word holds the promise of unlocking the doors to understanding, preventing, and curing cancer. Although methylation is a biochemical reaction that occurs millions of times a day in every cell in the body, it has not been very well studied. Its connection to cancer is now under intense scrutiny because methylation acts as a switch to activate or deactivate cancer genes (Mompalmer et al. 2001; Sasaki et al. 2001).

Cancer is fundamentally cellular growth gone wild. It can involve any organ of the body, but the one factor cancers have in common is that they are made of wildly proliferating cells. Normal cells replicate themselves, then stop. Cancer cells race through all normal checkpoints of cellular growth without stopping, and they cease to communicate with other cells. Striking new research shows that the same pathological mechanism causes all of this strange behavior: methylation dysfunction.

Methylation research has opened up new avenues for the detection, prevention, and the eventual cure of cancer (Cairns et al. 2001; Goessl et al. 2001; Weihrauch et al. 2001). It has been repeatedly shown that methylation-deficient diets and/or exposure to chemicals deplete methylation and cause cancer (Issa et al. 1996; Chen et al. 2001; Kim et al. 2001). Both events can be prevented and, to some extent, reversed by methylation-enhancing supplements, which include folic acid, SAMe, vitamin B12, and trimethylglycine (TMG) (Wilcken et al. 1985; Loehrer et al. 1996; Kuan et al. 2002). How can a person know if his/her level of methylation is below the healthy level? Homocysteine can be used as a rough guide to methylation status (until methylation testing becomes widespread). If homocysteine levels are elevated, methylation is

likely depressed (Yi et al. 2000).

DNA methylation is influenced by diet and methylation supplementation may reverse the progression of cancer in the early stages. It is not known, however, at what point cancer becomes irreversible. At this point, supplementation to enhance methylation would not be desirable inasmuch as methylation is also required for the synthesis of new cells, including cancer cells. For now, it is important to know that diet and exposure to chemicals can alter DNA methylation patterns and activate or deactivate genes involved in cancer (Fenech 2001). These alterations can be prevented, and potentially reversed, by dietary factors that enhance methylation, such as folic acid.

There are concerns that high doses of folic acid, vitamin B12, and S-adenosylmethionine (SAME) may not be beneficial to the cancer patient until the disease is brought under control. A consensus does not exist among experts, and we must thus rely on the consistency of the published scientific data indicating that moderate supplementation with methylation-enhancing agents would appear to prolong survival. A moderate approach would involve 800 mcg of folic acid, no more than 1000 mcg of vitamin B12, with SAME intake limited to around 800 mg daily. Some argue that only 200 mcg a day of folic acid and B12 be taken and SAME be avoided by those with active cancer. It should be reassuring; however, that all human (and animal) studies published to date show that folic acid improves survival.

The most recent human study of folic acid and human cancer was conducted on 42 patients afflicted with head and neck squamous cell carcinoma. Doctors evaluated the cancer patient's blood levels of folic acid and homocysteine in relation to two control groups without cancer. Compared to the control groups, the folate level in the cancer patients was 38% lower and the homocysteine level was 22% higher. The differences in serum levels of folate and homocysteine might arise from tumor development and consequent metabolic alterations, or might precede and promote tumor progression. If low folate is a risk factor for head and neck cancer, it might suggest a role for folate as a novel preventive agent both in patients with precancerous lesions and in patients with treated head and neck squamous cell carcinoma at risk for regional recurrence and second primary tumors (Almandori et al. 2002).

### **The Debate**

Proponents of dietary supplementation by cancer patients argue that high-dose multiple antioxidant supplements before and during conventional or experimental therapy may improve treatment efficacy by increasing tumor response and decreasing normal tissue toxicity (Prasad et al. 1999b). The proponents point out that even when a conventional therapy has proven cure rates, there exists the possibility of developing second cancers as a result of treatment. In addition, conventional therapy also produces toxicity during treatment that can be severe enough to cause discontinuation of certain therapeutic agents. Therefore, if dietary supplements can reduce the toxicity of normal cells, and/or increase the response of tumor cells to conventional therapy, there would be a significant improvement over the current management of cancer.

Critics argue that antioxidant supplements should not be used while treating cancer patients

with conventional therapy because they would protect cancer cells against free radicals that are produced by most anticancer agents (Labriola et al. 1999).

One way of approaching this dilemma is to observe the distinct differences of low-dose compared to high-dose antioxidants on cancer cells (Prasad et al. 1998; 1999b). Antioxidants such as vitamin A (and its drug analogs), vitamin E (tocopheryl succinate), vitamin C, and certain carotenoids, when used in high doses individually, have been shown to induce cell differentiation, growth inhibition, and apoptosis in rodent and human cancer cells *in vitro* and *in vivo* (Kline et al. 1995; Cole et al. 1997; Prasad et al. 1998; 1999b).

It appears that low-dose antioxidants might protect cancer cells against oxidative stress without inducing the desirable inhibitory effect (Park 1988; Cohen et al. 1995; Prasad et al. 1996). For example, vitamin C at a dose of 50 mcg/mL stimulates the growth of human parotid carcinoma cells and human leukemic cells in culture (Park 1988). Such low doses have no significant effect on the growth of other cancer cells (Prasad et al. 1996).

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***A Pilot Study to Assess Effects of Antioxidants in Combination with Carboplatin and Taxol on Tumor Response in Humans with Non-small Lung Carcinoma***

	<b>Chemotherapy alone (17 patients)</b>	<b>Chemotherapy + micronutrients (14 patients)</b>
Median follow-up	24 weeks	20 weeks
Median number of cycles	4 (6 cycles in 1 part)	3 (6 cycles in 6 parts)
Complete response	0	1
Partial response	2	7
Stable disease	1	3
Progressive disease	8	0
Death	6*	3**

*\*Five patients died of disease; one patient died of chemotherapy-induced toxicity.*

*\*\*One patient died of respiratory failure after pneumonectomy. The second patient died of a severe chest infection, which could not be treated with antibiotics in time because he resided in a remote area. The third patient was lost to follow-up after the second cycle of chemotherapy, and death reportedly occurred 4 months later at home (Pathak et al., 2002).*

***End table***

One study showed that a mixture of four antioxidants (13- *cis* -retinoic acid, sodium ascorbate,

tocopheryl succinate, and certain carotenoids) markedly inhibited the growth of human melanoma cells in culture (Prasad et al. 1994). Individually, these antioxidants had no effect on the growth of these tumor cells. Doubling the dose of one of the antioxidants (vitamin C) further reduced the growth of tumor cells *in vitro* (Prasad et al. 1994).

A mixture of four antioxidants was also more effective than the single antioxidant in reducing the growth of human parotid carcinoma cells in culture (Prasad et al. 1996). This observation is important because it experimentally indicates that a mixture of antioxidants could be more effective than a single antioxidant in reducing tumor growth. This study revealed that the use of multiple antioxidants might avoid the toxicity produced during treatment of certain human cancers with a single antioxidant at very high doses. A preliminary clinical trial in patients with non-small cell lung carcinoma demonstrated that the tumor response of patients receiving carboplatin and Taxol together with high doses of vitamin C, vitamin E, and beta-carotene was better than in patients receiving carboplatin and Taxol alone (Table 1).

High-dose antioxidants have been shown to inhibit the growth of different rodent and human cancer cells *in vivo* and *in vitro* (Cole et al. 1997; Prasad et al. 1998; 1999a; 1999b). For example, tocopheryl succinate (a form of dry vitamin E powder) induces apoptosis in human prostate cancer cells but not in normal prostate cells *in vitro* (Isreal et al. 2000). In addition, tocopheryl succinate has been shown to decrease accumulation of mitotic (dividing) cells in three human cancer cell lines but not in normal human fibroblasts (Jha et al. 1999). Tocopheryl succinate also induces chromosomal damage in human cervical cancer cells and in human ovarian cancer cells but not in normal human fibroblasts (Kumar et al. 2002). High doses of individual antioxidants such as vitamin A and its analogs, vitamin C, beta-carotene, and vitamin E have been used in rodents and humans without any effects on proliferating cell systems (Cameron et al. 1979; Seifter et al. 1984; Dreno et al. 1993; Garewal 1995; Lippman et al. 1995; Meyskens 1995; Schwartz 1995; Chinery et al. 1997; Malafa et al. 1999; Prasad et al. 1994; Prasad et al. 1999a), while exhibiting varying levels of antitumor activity.

Critics of antioxidant supplements point to a study demonstrating that tumor cells *in vivo* are more sensitive to antioxidant deficiency (vitamin A and E) than normal cells with respect to growth inhibition (Salganik et al. 1999). If tumor cells exhibit a greater sensitivity to a deficiency of antioxidant vitamins than normal cells, then it would make sense to try to temporarily induce an antioxidant deficiency in the body. The problem in trying to achieve a vitamin E or vitamin A deficiency is that this could cause damage to healthy tissues--some of which could be irreversible. It is also difficult to induce the kind of severe vitamin E deficiency in humans needed to adequately starve cancer cells of this antioxidant (additionally, a vitamin E deficiency has been correlated with an increased incidence of other cancers) (Woodson et al. 2002; Lagiou et al. 2001; Hammerer et al. 2000; Mannisto et al. 1999; Bohlke et al. 1999; Zhu et al. 1996).

It is interesting to note that antioxidant treatment for a short period (a few hours) may not inhibit the growth of cancer cells, whereas the treatment of cancer cells for a longer period of time (24 hours or more) with the same dose of antioxidants may cause growth inhibition. There is also variation on the growth inhibitory effects of antioxidants based on the time they are given in relationship to other cancer therapies. Furthermore, depending on the types of tumor cell,

antioxidants may or may not show benefit. Vitamin A, for instance, induces cell differentiation in some tumor cells of epithelial origin (Sporn et al. 1983; Carter et al. 1996), whereas beta-carotene and tocopheryl succinate do not. Tocopheryl succinate and beta-carotene induce differentiation in murine melanoma cells (Prasad et al. 1982; Hazuka et al. 1990), whereas vitamins C and A do not. Vitamin C inhibits the growth of tumor cells but does not cause differentiation (Cameron et al. 1979; Prasad et al. 1979). These studies show that antioxidants do not produce similar effects on different types of cancer cells.

Depending on the type of therapy used, antioxidants may affect cancer cells in many different ways. For example, studies reveal that vitamin C, tocopheryl succinate and acetate, vitamin A (and its analogs), and certain carotenoids enhanced the growth inhibitory effect of most types of radiation and chemotherapy on some cancer cells in culture (Prasad et al. 1999b). The magnitude of this enhancement depended on the dose and form of the nutrient, the dose and type of chemotherapy agent, and the type of tumor cell. Tocopheryl succinate, for instance, induced differentiation of melanoma cells in culture.

Retinoid drugs have been successfully used in human cancer studies. Several mechanisms of action of antioxidants on cancer cells *in vitro* have been proposed. For example, high-dose antioxidants inhibit expression of the RAS oncogene (Amatruda et al. 1985; Prasad et al. 1990; Schwartz 1995) and the activity of protein kinase C (Mahoney et al. 1988; Gopalakrishna et al. 1995). Changes such as this are considered growth inhibitory signals for cancer cells.

These variable factors help explain why one group of scientists can say antioxidants have no effect (when looking only at short-term studies), and another group of scientists looking at the same antioxidants can claim a benefit (when looking at longer-term studies, at different dosing schedules relative to the use of other therapies, or at tumors of different origins).

Studies looking at different types of tumors show encouraging results. Tocopherol succinate, for instance, enhanced the effect of radiation treatment on neuroblastoma cells in culture, and tocopherol acetate enhanced the effect of the chemotherapy drug vincristine on neuroblastoma cells in culture. Vitamin C was shown to enhance the effect of the chemotherapy drug 5-fluorouracil (5-FU) on neuroblastoma cells in culture.

There are a few *in vivo* (whole body) studies that support the concept that antioxidants selectively enhance the effect of conventional therapy on tumor cells by increasing tumor response. Retinyl palmitate (vitamin A) or synthetic beta-carotene at doses 10 times higher than the recommended daily allowance (RDA), in combination with radiation or the drug cyclophosphamide, increased the cure rate from 0 to more than 90% in mice with transplanted breast cancer (Seifter et al. 1984). A study using a thiol-containing antioxidant and a water-soluble vitamin E analog demonstrated the enhanced antitumor effects of the drugs 5-FU and doxorubicin *in vitro* against several cancer cell lines, as well as the effect of 5-FU *in vivo* against two colorectal cancer cell lines (Chinery et al. 1997). The combination of the vitamin A analog drug Accutane and the immune modulating drug alpha-interferon enhanced the levels of radiation-induced growth inhibition in human head and neck squamous cell carcinoma *in vitro*

(DeLaney et al. 1996).

Opponents of cancer patients taking dietary supplements point out that the effect of individual antioxidant vitamins in combination with radiation or chemotherapy agents have not been systematically tested in human tumors *in vivo*. Although this is true, there are studies indicating that certain antioxidants in combination with radiation and chemotherapy may be beneficial. In one study, 18 nonrandomized patients with small cell lung cancer received multiple antioxidant treatment with chemotherapy and/or radiation. This type of lung cancer has a very poor prognosis. The median survival time was markedly enhanced, and patients tolerated chemotherapy and radiation therapy well (Jaakkola et al. 1992).

Similar observations were made in private practice settings (Lamson et al. 1999). A randomized trial with non-small cell lung carcinoma patients showed that tumor response in groups receiving chemotherapy plus multiple antioxidants was better than in groups receiving chemotherapy alone. Another study showed that beta-carotene supplementation reduced radiation- and chemotherapy-induced oral mucositis without interfering with their efficacy on tumor cells (Mills 1988). A combination of retinoic acid and interferon enhanced the effect of radiation therapy on locally advanced cervical cancer (Lippman et al. 1993). In a mouse study, a mixture of antioxidants reduced bone marrow suppression caused by radiation and immune therapies without interfering with the treatment efficacy in reducing tumor growth (Blumenthal et al. 2000).

Critics of cancer patients taking antioxidants remain troubled that many types of conventional therapies induce tumor cell death, in part, by generating excessive amounts of free radicals. Their concern is that high-dose antioxidant supplementation during standard cancer therapy could be harmful since the antioxidants might protect both normal and cancer cells against the cell-killing effects of tumor therapeutic agents (Labriola et al. 1999). This theory is contradicted by studies showing that vitamin C, tocopheryl succinate, and Accutane (vitamin A analog) enhanced the growth inhibitory effect of radiation and certain chemotherapy agents on tumor cells in culture and *in vivo* (Prasad et al. 1998; 1999b). This demonstrated that antioxidants do not protect cancer cells against the growth-inhibitory effect of conventional therapy and may in fact enhance the growth inhibitory effects on tumor cells.

## **Conclusions**

Our review of the published scientific literature and conference reports would appear to indicate that cancer patients might derive enormous benefits by taking dietary supplements. We are troubled, however, by the knowledge that cancer is an extremely complex disease that defies simple solutions. We know that every person's cancer is different from another's and that even cancer cells within a given tumor show marked molecular differences (heterogeneity).

Cancer is unlike any other disease inasmuch as cancer cells often benefit from many of the same nutrients needed by healthy cells. Although cellular studies show that certain nutrients interfere with cancer cell propagation, these data are not yet conclusive.

We have gone to enormous lengths to present the facts so that the cancer patient can make an informed decision about using supplements. What we did not include in this chapter were

comments from other cancer experts who have used high-potency supplements for decades in their practices. If we were to include comments from everyone who wanted to contribute to this article, it would have been heavily biased in favor of cancer patients using dietary supplements.

On the flip-side, we were also concerned about the power of negative bias, especially as it relates to folic acid. Some researchers do not believe a cancer patient should take folic acid, yet every published study shows cancer patients are surviving much longer when consuming folic acid supplements and have higher levels of folic acid in their blood. The same appears to be true for antioxidants.

Many experts equivocate when it comes to antioxidant supplements. They acknowledge that cell culture, animal, and human studies indicate that antioxidants would both help to inhibit cancer cell propagation and protect the body against therapeutic toxicities, malnutrition, immune dysfunction, and so forth. They are concerned, however, that antioxidants protect so well that they may interfere with apoptosis (programmed cell death) in cancer cells.

Contradicting this negative theory are the many studies showing that the tocotrienols (a potent form of vitamin E) induce significant inhibitory effects against active cancer cell lines. The tocotrienols may be nature's most powerful natural antioxidant, yet when certain types of cancer cells are exposed to them, a direct antiproliferative effect occurs.

To give you an idea of the debate that goes back and forth, one only has to look at studies on alpha tocopheryl succinate (dry-powder vitamin E). Some argue against taking antioxidants during radiation therapy because radiation kills cancer cells by generating massive free radicals. Yet the most recent study on this subject showed that tocopheryl succinate enhanced radiation damage to ovarian and cervical cancer cells but protected healthy cells! This study showed that both cancer and normal cells absorbed a similar amount of tocopheryl succinate, but only the cancer cells were sensitized to the radiation by this form of vitamin E. The doctors who conducted this study concluded that: "The use of alpha tocopheryl succinate during radiation therapy may improve the efficacy of radiation therapy by enhancing tumor response and decreasing some of the toxicities on normal cells" (Kumar et al. 2002).

A serious side effect from cancer radiation therapy is fibrosis to healthy tissues. Fibrosis is an inflammatory condition that causes progressive scarring (necrosis) to healthy tissue that can lead to debility or death. Antioxidants have not only been shown to prevent fibrosis, but also reverse it. Based on the published research, it would appear that patients undergoing radiation procedures might derive therapeutic and protective benefits if they consumed the proper antioxidants before, during, and after therapy. The downside, critics argue, is that long-term survival studies of radiation patients supplementing with high doses of antioxidants are lacking (Letur-Konirsch et al. 2002).

The individual stricken with cancer today needs a definitive answer about what dietary supplements are appropriate, when and how much should be taken, or whether they should be taken at all. The Life Extension Foundation is determined to make definitive recommendations but cannot make a generalized conclusive statement that accurately pertains to the use of every

dietary supplement in every type of cancer during every conventional therapy. In other words, there is inadequate substantiation to address how every single supplement might affect each individual cancer patient. The evidence presented, however, speaks for itself.

The most comprehensive report dealing with this subject was published in the October 2001 issue of the Journal of the American College of Nutrition . Below is an excerpt from this paper entitled "Scientific Rationale for Using High-Dose Multiple Micronutrients as an Adjunct to Standard and Experimental Cancer Therapies" (Prasad et al. 2001):

We have hypothesized that high-dose multiple micronutrients, including antioxidants, as an adjunct to standard (radiation therapy and chemotherapy) or experimental therapy (hyperthermia and immunotherapy), may improve the efficacy of cancer therapy by increasing tumor response and decreasing toxicity. Several in vitro studies and some in vivo investigations support this hypothesis. A second hypothesis is that antioxidants may interfere with the efficacy of radiation therapy and chemotherapy. This hypothesis is based on the concept that antioxidants will destroy free radicals that are generated during therapy, thereby protecting cancer cells against death. None of the published data on the effect of antioxidants in combination with radiation or chemotherapeutic agents on tumor cells supports the second hypothesis. Scientific rationale in support of a micronutrient protocol to be used as an adjunct to standard or experimental cancer therapy is presented.

The various cancer protocols in this book provide the cancer patient with a wide range of therapeutic and lifestyle choices that have been shown to provide significant benefit. Life Extension urges cancer patients to embark on a multimodality treatment program that is practical from an individual standpoint.

### **Disclaimer**

This information (and any accompanying printed material) is not intended to replace the attention or advice of a physician or other health care professional. Anyone who wishes to embark on any dietary, drug, exercise, or other lifestyle change intended to prevent or treat a specific disease or condition should first consult with and seek clearance from a qualified health care professional.