



Clinical Nutrients in Cancer Therapy:

A Scientific Review and Perspective

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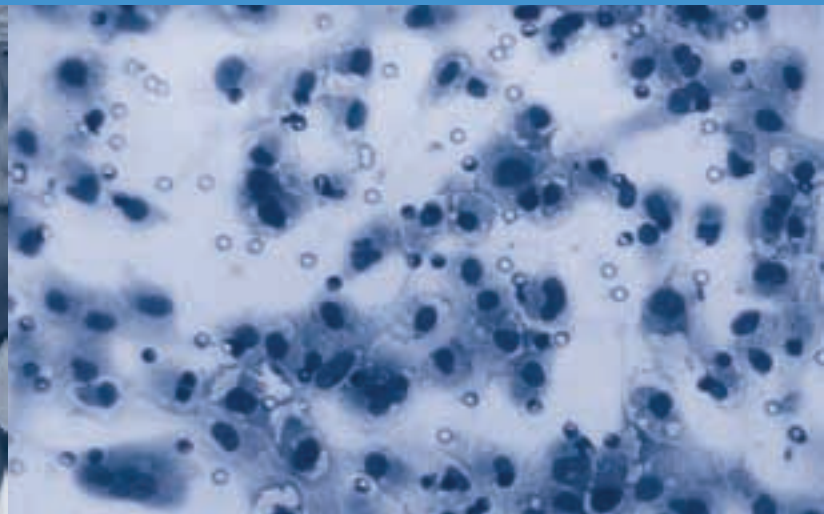


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The Clinical Effects of Cellular Nutrients in Cancer: A Scientific Review and Perspective

Introduction

Despite the extensive use of conventional therapies, cancer mortality has not decreased over the last few decades; on the contrary, it is increasing (Jemal, et al., 2002; Howe, et al., 2001). Standard cancer treatments generally involve a combination of surgery, multiple chemotherapeutic agents, and ionizing radiation. Apparently, these conventional approaches have not been successful in controlling cancer. Moreover, they are associated with the severe toxicity of chemotherapeutic agents, with the development of drug resistance by cancer cells, and with genotoxicity, giving rise to new cancers.

This situation demands a revision of current approaches and the development of new strategies in the treatment of cancer aimed at increasing the efficacy of treatments, as well as reducing drug and radiation toxicity, and developing new therapies. In this regard, the use of micronutrients in therapeutic doses as an adjuvant or outright curative therapy in the treatment of cancer offers the most promise. In fact, approximately 80% of patients diagnosed with cancer seek alternative therapies, which include antioxidants and other essential nutrients. However, some representatives of mainstream medicine have attacked supplements of vitamins and other essential nutrients as potentially harmful. These attacks are unjustified and are being published despite scientific evidence showing that cancer patients who use supplements do benefit from them.

In the search for effective solutions to cancer, the work of Rath, et al. (1992) provides a new perspective in the therapeutic use of essential nutrients, such as vitamin C and lysine, in the control of cancer growth and metastasis. Further research in this direction at the Dr. Rath Research Institute of Cellular Medicine under the direction of Dr. Aleksandra Niedzwiecki has led to the development of a particularly effective natural approach to the control of cancer based on nutrient synergy.

In this documentation, we summarize the available evidence that this nutrient synergy is the most effective way currently available to control the critical processes of cancer, including metastasis, angiogenesis, cell proliferation and apoptosis. We also review the available clinical information about the use of individual nutrients in cancer therapy and provide an encouraging perspective on the application of nutrient synergy in clinical medicine.

The Physiological Targets of Effective Cancer Therapy

Effective cancer therapy should achieve one or more of the following objectives (Figure 1):

- A. Prevention of the metastasis (tissue invasion) of cancer cells
- B. Prevention of the replication of cancer cells
- C. Prevention of angiogenesis (new blood vessel formation) in tumors
- D. Stimulation of apoptosis (programmed cell death) in cancer cells and destruction of cancer cells

The most critical aspect of cancer in terms of patient survival is stopping cancer metastasis. This process, as well as many other aspects of neoplasia, are closely connected to the interaction between cancer cells and the extra-cellular matrix (ECM). Various nutrients primarily affect the properties of ECM; among them are vitamin C, as well as the amino acids lysine and proline, which play the most important role. The literature is also replete with clear evidence that other nutrients can also modify or regulate various stages in cancer promotion and the progression of cancer cells. Therefore, we critically evaluated the published evidence regarding the efficacy of various nutrients important in achieving one or more of the above objectives of effective cancer therapy.

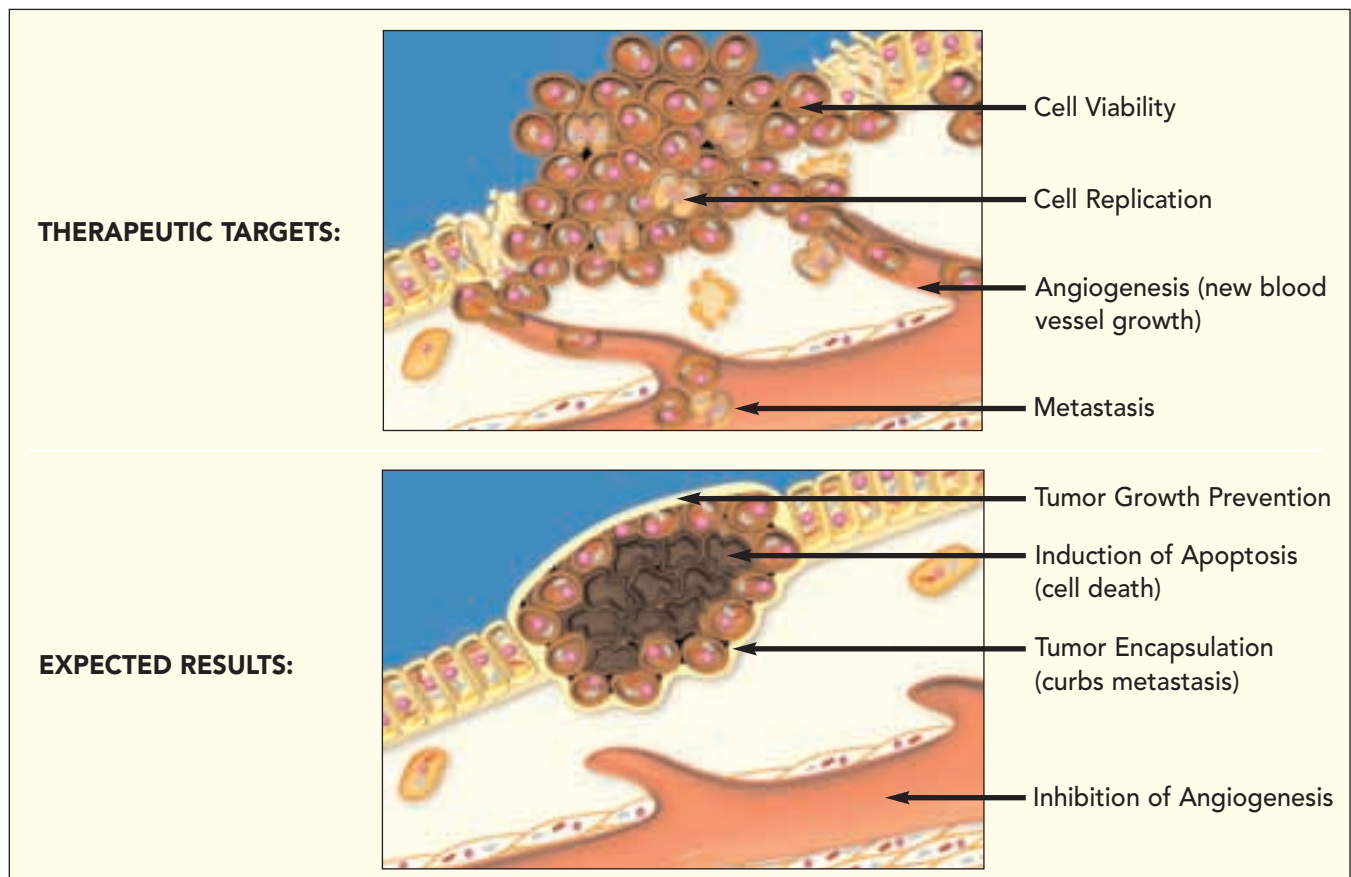


Figure 1

Individual Nutrients in Cancer Therapy

1. Vitamin C

Vitamin C (ascorbate) has been the most researched and applied nutrient in cancer. Since the time Cameron reported that vitamin C had beneficial effects on cancer patients (Cameron and Campbell, 1974), several studies have been published regarding the therapeutic potential of this nutrient (Meadows, et al., 1991; Tsao, 1991; Liu, et al., 2000; Alcain, et al., 1994).

In 1978, Cameron and Pauling reported the results of a clinical study in Scotland in which 100 terminal cancer patients were given 10 g of supplemental sodium ascorbate. The survival time of these patients was compared with a control group of 1,000 patients that did not receive any ascorbate. The results showed that patients in the ascorbate-treated group had an increased average survival time of 321 days as compared to the matched control. Twenty-two patients in the ascorbate-treated group of 100 patients survived for more than one year (22%) versus only four out of 1,000 in the control group (0.4%). This study, based on the hospital records of the cancer patients, was retrospective, not prospective. As a result, it was criticized for not being free from bias with respect to patient selection (Moertel, et al., 1985).

Moertel and his group conducted prospective double-blind studies using 10 g of vitamin C in patients that had not received prior chemotherapy. All the selected patients were in the advanced stage of large bowel cancer, and were considered otherwise untreatable; however, the study could not establish any treatment benefits. Cameron and Campbell (1991) also conducted prospective studies in cancer patients. In one study, patients in the vitamin C group received 10 g of sodium ascorbate daily. Many patients in the vitamin C group were administered the designated dose of ascorbate intravenously for the first 10 days. The survival time for 50% of the patients in the vitamin C group was 343 days. For the control group, the mean survival time was 180 days. The investigators stated that these results indicated that patients receiving supplemental vitamin C lived longer than those who did not. They also found a positive correlation between the plasma vitamin C levels of patients and their survival time. The inverse relationship between plasma vitamin C levels and cancer-related mortality was also later confirmed by Khaw, et al. (2001). While these results were encouraging, they were not compelling enough to be accepted by mainstream clinical medicine.

The diverging results among various trials are intriguing. A review of some in vitro studies will be helpful in the interpretation of these differences. In an in vitro study, vitamin C is added to cancer cells cultured in media. Cell growth is measured by counting the number of cancer cells after pre-designated incubation periods. The vitamin C levels effective in inhibiting the proliferation of cancer cells in various studies ranged between 400 μM and 1 mM (Leung, et al., 1993; Riordan, et al., 1995; Koh, et al., 1998; Netke, et al., 2003; Harakeh, et al., 2004).

Can these vitamin C levels be obtained in the human body? Vitamin C blood concentration depends on its rate of absorption from the digestive tract and its rate of elimination by the kidneys. When 1,000 mg of ascorbic

acid was given orally daily, the steady-state plasma level of ascorbic acid was about 80 μM (Levine, et al., 1996). The studies also indicated that with higher intake, such as 2,500 mg daily, the plasma levels of ascorbic acid could reach the 100 μM range. It can thus be seen that reaching the required levels of ascorbic acid in the blood sufficient for inhibiting cell proliferation is difficult to achieve by oral administration.

The question then becomes whether the desired plasma levels of ascorbate can be achieved by intravenous injections without any adverse effects to patients. In the studies reported by Riordan, et al. (1995), patients were given ascorbic acid intravenously. The patients were first screened for any adverse reactions to ascorbic acid by receiving smaller doses intravenously. They were then administered 115 g of ascorbic acid dissolved in one liter of Ringer's Lactate by drip over an eight-hour period. Each patient was given 39 such infusions over a period of 13 weeks. Between infusions, patients received ascorbic acid orally to bowel tolerance (approximately 10 g daily). Plasma ascorbic levels as high as approximately 10 mM (180 mg/dl) were obtained in these studies, and there was no progression of disease during the period of administration of vitamin C. Such high ascorbate concentrations are still within physiologically recognized ranges, since it has been reported that its intracellular concentrations in lymphocytes under different oral supplementation are approximately 4 mM (Levine, et al., 2001) and in activated lymphocytes, ascorbate levels can reach 10 mM (Victor, et al., 2001). It is thus clear that high plasma levels of vitamin C are necessary to achieve beneficial results in cancer patients, and these levels can be achieved by intravenous injection of vitamin C.

In the studies of Moertel, et al. (1985), vitamin C was given orally, not intravenously, as was done in the studies reported by Cameron and Campbell (1995). The difference in the mode of administration of vitamin C might explain the difference in the outcome of the studies. Parenteral administration of ascorbic acid is slowly finding acceptance in the conventional medical community. Drisko, et al. (2003), of the Division of Gynecologic Oncology at the University of Kansas Medical Center (USA), used 60 g of ascorbate administered parenterally twice a week, in addition to megadoses of antioxidants given orally, in two ovarian cancer patients. This treatment achieved satisfactory results, and the patients had remained cancer-free for more than three years by the time the report had been published. Again, these studies were not able to provide compelling results on the therapeutic value of vitamin C in cancer to be accepted by mainstream medicine.

1a. Possible Anti-Cancer Mechanisms of Vitamin C

It has been generally assumed that vitamin C functions as an anti-cancer agent because of its antioxidant activity, that is, by quenching the reactive oxygen species (ROS). Now it is known that vitamin C exercises its effects in several other ways.

The studies of Maramag, et al. (1997) with prostate cancer cells indicate that vitamin C inhibits cell division and growth by the production of hydrogen peroxide. Singlet oxygen scavengers, such as sodium azide and hydroquinone, and hydroxyl radical scavengers, such as d-mannitol and dl-alpha-tocopherol, did not counteract the effects of ascorbic acid on thymidine incorporation, suggesting that vitamin C-induced changes were not related to ROS.

Ultra-structural and cell surface studies on squamous cell carcinoma and basal cell carcinoma induced by 3-methylcholanthrene have revealed that ascorbic acid significantly affected cell growth and differentiation. Multiple effects, such as cytolysis, cell membrane disruption, mitochondrial alterations, nuclear and nucleolar reduction and increased phagolysosome formation, were observed in cancer cells following vitamin C administration (Lupulescu, 1992).

Vitamin C has been shown to positively modulate several genes, such as fra-1 glutathione S-transferase pi (GSTpi) and Mut L homologue-1 (MLH-1), in human cells. It was demonstrated that MLH-1, as well as its downstream target p73, can be positively modulated by this vitamin. The upregulation of two relevant mRNAs was observed after only two hours of exposure to ascorbate, and continued to increase during 16 hours of treatment. The modulation of MLH-1 and p73 gene expression improved cellular susceptibility to apoptosis triggered by the DNA-damaging agent Cisplatin, as well as p73. This activity was independent of p53 (Catani, et al., 2002).

Our studies in collaboration with Dr. Harakeh and others (Harakeh, et al., in preparation) indicate that vitamin C can exert apoptotic effects on several leukemia cell lines, including HTLV-1 infected leukemia cells, by upregulating the expression of pro-apoptotic p53, p21, and Bax and downregulating the protein Bcl-2a expression.

Vitamin C plays a critical role in the production and structure of collagen fibers and largely defines the composition of ECM. Consequently, vitamin C can increase ECM strength, creating an encapsulating effect that can hinder cancer cell spread (Rath and Pauling, 1992; Roomi, et al., 2003).

1b. Specific Concerns Regarding Vitamin C in Cancer

- Vitamin C Acting as a Pro-oxidant in Certain Circumstances

Various in vitro studies have indicated that the interaction between vitamin C and free catalytically active metal ions could contribute to oxidative damage by the production of hydroxyl and alloxyl radicals. In essence, this means that ascorbic acid can act as a pro-oxidant instead of an antioxidant in the body.

Carr and Frei (1999) reviewed several studies investigating the effects of vitamin C incubated in the presence and absence of metal ions on oxidative damage to DNA, lipids, and proteins. These studies provided compelling evidence for the antioxidant protection of lipids by vitamin C in biological fluids and in animals and humans, both with and without iron supplementation. Although the data on protein oxidation in humans was sparse and inconclusive, the available data in animals consistently confirmed the antioxidant role of vitamin C. The review, which evaluates several relevant studies, does not support the statement that vitamin C acts as a pro-oxidant in the body.

- Vitamin C and the Production of Genotoxins

Fear has been spread that higher intakes of vitamin C can cause the production of genotoxins. This apprehension stems from the studies of Lee, et al. (2001). These researchers reported that intake of 200 mg of vitamin C per day induced the decomposition of lipid hydroperoxides to endogenous genotoxins. These conclusions were reached based on in vitro studies in which very high levels of lipid hydroperoxides (400 micromol/liter) were used. Such high levels are not physiologically relevant. The physiological blood levels of hydroperoxides are an order of magnitude lower, ranging only between 10-500 nmol/liter. The probability of obtaining even these levels of hydroperoxides in vivo is low because high intake of vitamin C augments glutathione in human lymphocytes, which inhibits lipid peroxidation (Lenton, et al., 2003). Levine, et al. (2001) also reported that higher levels of vitamin C intake did not produce higher levels of lipid peroxides.

- Vitamin C and Mutagenic Effects

Podmore, et al. (1998) claimed that dietary vitamin C intake of 500 mg/day may exert pro-oxidant and mutagenic effects in humans based on the increase in number of modified DNA bases in lymphocytes, in particular 8-oxoadenine. These studies indicated, at the same time, a significant decrease in 8-oxoguanine concentrations. 8-oxoguanine is an important mutagenic lesion in DNA. Any decrease in the concentration of 8-oxoguanine indicates that vitamin C can protect DNA from mutagenic alterations.

The study findings of Podmore's group have to be taken with reservations because the method of estimation of the oxo-compounds used was not reliable. It is known that these compounds can be formed during the processing of samples.

1c. Safety of High Intakes of Vitamin C

- Kidney Stone Formation

Concerns have been raised about the possibility that higher intakes of vitamin C can lead to the formation of renal calcium oxalate stones. A thorough search conducted by Goodwin and Tangum (1998) of the medical literature found no reliable articles supporting this concern. On the contrary, three case-controlled studies did not show a clear association between ascorbate intake and excretion and stone formation (Cowley, et al., 1987; Power, et al., 1984; Felstrom, et al., 1989).

The positive association between vitamin C and kidney stones reported by some workers may be because older assays for urinary oxalates allowed the conversion of urinary ascorbic acid to oxalates during the storage and processing of the samples.

It was reported by Wandzilak, et al. (1994) that vitamin C added to the urine was converted into oxalic acid and the increase in the amount of oxalates in the urine of volunteers taking large doses of vitamin C (up to 10 g) could be entirely accounted for by the amount of vitamin C excreted in the urine converted to oxalates.

In a large-scale Harvard Prospective Health Professional Follow-Up Study in 45,000 men, those groups in the highest quintile of vitamin C intake (>1500 mg/day) had a lower risk of kidney stones than the group in the lowest quintile (Curhan, et al., 1996).

A review of various studies led Gerster (1997) to conclude that the intake of high doses of vitamin C does not increase the risk of calcium oxalate kidney stones. These findings were re-confirmed in the studies conducted in the cohort of about 85,500 people (Curhan, et al., 1999).

- Adverse Effects

There have been some reports of the possible toxic effects of vitamin C, but critical analyses of these papers have failed to substantiate them (Diplock, 1995; Bendich, 1992). It is worth mentioning here that a dose of ascorbate as high as 115 g/day administered by an intravenous route over eight hours and 39 times in a period of 13 weeks did not produce any adverse effects in cancer patients (Riordan, et al., 1995). Megadoses of vitamin C alone or combined with other antioxidants have been used in several other clinical studies without any toxic effects to the patients (Moertel, et al., 1985; Cameron and Campbell, 1991; Lockwood, et al., 1994; Walker, et al., 2002; Drisko, et al., 2003).

Some persons may experience bowel intolerance to high doses of vitamin C. The intake of vitamin C should, therefore, be gradually increased. Intake should be limited only to the level of bowel tolerance.

2. Green Tea Components (EGCG) and Green Tea Extract (GTE)

Over the past few years, several studies have indicated that green tea extract has tremendous potential in the treatment of cancer (Hare, 2001). The active constituents of green tea are epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate. Of these four, epigallocatechin gallate (EGCG) shows the greatest potency. There are reports that suggest the synergistic activity of all these catechins when green tea extract is used as such.

- *Epigallocatechin Gallate (EGCG)*

EGCG has been shown to be a promising agent in controlling angiogenesis, metastasis, and other aspects of cancer (Hare, 2001). The development of the blood supply (angiogenesis) is crucial to the growth and metastasis of cancer, and the factors involved in this process are complex. The secretion of vascular endothelial growth factor (VEGF), which stimulates the proliferation of vascular endothelial cells and the synthesis of activators of matrix metalloproteinases (MMPs) that result in the digestion of extracellular matrix, and the migration of endothelial cells that form tube structures (new blood vessels) are critical. The high activity of MMPs also facilitates the spread and tissue invasion of cancer cells.

In vitro studies, EGCG, the principal constituent of green tea extract, inhibited increased VEGF expression and promoter activity induced by serum starvation of HT29 human colon cancer cells (Jung, et al., 2001). The decrease in VEGF expression would consequently reduce angiogenesis. In other studies, it was shown that tube formation by human umbilical vein endothelial cells (HUVEC) was inhibited by EGCG (Singh, et al., 2002). Tube formation by HUVEC represents the process of angiogenesis in a laboratory model.

EGCG was also shown to inhibit the activities of gelatinases – matrix metalloproteinases 2 and 9 (MMP-2, MMP-9) – over-expressed in cancer and angiogenesis. Similarly, tumor cell invasion of the reconstituted basement membrane matrix was reduced by 50% with EGCG at concentrations equivalent to those obtained in the plasma of moderate green tea drinkers. The concentrations of EGCG active in restraining proliferation and inducing apoptosis of transformed cells were more than 100 times lower than those reported for normal cells (Garbisa, et al., 2001).

EGCG also reduced the migration of HUVEC through the Matrigel membrane. This was found to be due to the modulation of MMP activity by EGCG. It has been shown that EGCG interferes with the activity of MMP-2 on several levels. First, it reduces the secretion of ProMMP-2 (an inactive form of MMP-2). ProMMP-2 is activated from its pro-enzyme form to an active form by another transmembrane enzyme, MT1-MMP-2 (Singh, et al., 2002). EGCG significantly reduces the amount of MT1-MMP-2 formed by acting at the gene and protein expression levels (Annabi, et al., 2002).

Our studies have shown that EGCG administered in non-toxic concentrations to leukemia cells (Jurkat and C91Cl) and HTLV-1 infected leukemia cells (HUT102 and CEM) inhibited cell proliferation and triggered cell apoptosis as confirmed by flow cytometry, Western Blot, and other assays (Harakeh, et al., a, b).

- *Green Tea Extract (GTE)*

Sartippour, et al. (2001) showed that green tea extract (GTE) and its catechin components were effective in inhibiting breast cancer and endothelial cell proliferation in cell culture studies. GTE was also found to suppress cell growth and induce apoptosis in human prostate cancer cells DU145 (Chung, et al., 2001).

The catechins in GTE were shown to inhibit the growth of human colon cancer cells HCT116 (Uesato, et al., 2001) and inhibit MMP activity and pro-MMP activation (Demeule, et al., 2000). The inhibition of MMPs adversely affects cancer cell invasion of ECM and thus interferes with metastasis.

Several independent research studies have shown that the consumption of green tea reduces the development of cancer in many animal models. In one study (Jung, et al., 2001), athymic nude mice were inoculated subcutaneously with HT29 cells. The animals were then treated with 1.5 mg of EGCG injected i.p. daily. Treatment with EGCG reduced tumor cell proliferation by 27%, inhibited tumor growth by 58%, lowered micro-vessel density by 30% and increased tumor cell apoptosis by 1.9 fold and endothelial cell apoptosis by threefold relative to the control.

In mice, GTE was shown to suppress xenograft size and decrease tumor vessel density (Sartippour, et al., 2001). EGCG also inhibits the process of angiogenesis. Thus, there is very strong evidence that GTE increases apoptosis, depresses cancer cell proliferation, reduces cancer cell invasion and inhibits angiogenesis.

3. N-Acetyl Cysteine

N-acetyl cysteine (NAC) is a derivative of the amino acid L-cysteine. It supplies bioavailable cysteine necessary for the replenishment of glutathione (GSH), a tripeptide (gamma-y-glutamyl-cysteine-glycine) that plays a variety of physiological roles, including the regulation of signal transduction (Schreck, 1991), intracellular defense against oxidative stress (Meister, 1994), and other functions important in the neoplastic process.

Colon cancer cells manifest increased expression of the insulin-like growth factor receptor (IGF-IR). Ligand-activated IGF-IR inhibits apoptosis. It has been demonstrated that NAC downregulates the expression of IGF-IR in HT29, SW480, and LoVo colon-adenocarcinoma cell lines. Signaling through IGF-IR mediates cell cycle progression from G1 phase to S phase. Any interference with this signaling would lead to a reduction in the multiplication of cancer cells. NAC, at 40 μ M level in cell culture studies, reduced the proliferation of colon cancer cells to 20% of the control. This was found to be due to the effect of NAC on the reduced expression of IGF-R levels on the cell surface of cancer cells (Kelly, et al., 2002).

In a study on T24 human bladder cancer cells, NAC reduced the production of MMP-9 and also caused the inhibition of MMP-9 activity (Kawakami, et al., 2001). NAC is known to completely inhibit gelatinolytic activity, metalloproteinases, and the chemotactic and invasive activities of tumor cells (Morini, et al., 1999). Other studies have shown that NAC is able to reduce the invasive and metastatic potential of melanoma cells and inhibit tissue invasion of endothelial cells (Tosetti, et al., 2002) and fibrosarcoma cells (Yoon, et al., 2001). NAC also strongly inhibited neo-vascularization of Matrigel sponges in response to Kaposi's sarcoma cell products (Cai, et al., 1999).

NAC has shown promising results in athymic nude mice bearing MDA-MB-435 xenografts when treated with synthetic NAC daily for eight days. NAC treatment resulted in endothelial cell apoptosis and reduction in microvascular density (Agarwal, et al., 2004). In animal models of carcinogenesis, NAC used on pre-established tumors produced a sharp inhibition of tumor growth with regression of tumors in 50% of the cases (Albini, et al., 2001).

NAC prevented *in vivo* carcinogenesis in nude mice that were injected with malignant murine melanoma cells. It also reduced the number of lung metastases (Morini, et al., 1999). The experimental evidence cited above indicates that NAC can be useful in reducing cancer cell proliferation and cancer cell invasion of ECM (metastasis) and the induction of apoptosis and reduction of angiogenesis.

4. Selenium

The trace mineral selenium is not itself an antioxidant, but within cells it is incorporated into selenoproteins, some of which have antioxidant functions (i.e. glutathione peroxidase). In addition, selenium may directly induce tumor cell apoptosis and inhibit cancer cell spread in the tissues.

Selenium-inhibited Matrigel invasion by HT1080 human fibrosarcoma cells prevented the adhesion of the cells to the collagen matrix. Such an adhesion to ECM is a prerequisite for the process of migration. Selenium also reduced the production of MMP-2 and MMP-9 by fibrosarcoma cells (Yoon, et al., 2001). The inhibition of invasion through the Matrigel membrane was possibly accounted for by these two factors: non-adhesion of cells to the cellular matrix and a reduction in the production of MMPs.

Selenium interfered with the activity of MMP-9 and reduced the migration of endothelial cells through ECM (Tosetti, et al. 2002; Morini, et al., 1999). Selenium also decreased MMP-2 expression in human umbilical vein endothelial cells and secretion of VEGF in human prostate (DU145) and breast cancer cell lines (MCF-7 and MDA-MB 468), the steps critical for the reduction of angiogenesis.

Another interesting observation is that selenium reduced the expression of urokinase-type plasminogen activator (Yoon, et al., 2001). This activator is expressed in very high concentration by many cancer cells, and it plays an important role in converting inactive Pro-MMP enzymes into active MMP enzymes. The non-conversion of Pro-MMP to MMP would adversely affect the process of tissue invasion and, consequently, local spread and metastasis.

Selenium metabolite (selenodiglutathione) causes induction of the Fas ligand. The attachment of the ligand to the receptor causes selective activation of the Fas pathway in carcinomas. Activation of the pathway could be directly responsible for the destruction of cancer cells by apoptosis or by turning them into an easy target for attacks by immunological responses (Fleming, et al., 2001). The studies clearly show that selenium has the ability to prevent cancer cell invasion of ECM (metastasis) and affect the processes of angiogenesis and apoptosis.

5. Arginine

Arginine is conditionally an essential amino acid. It is likely to be deficient under conditions of stress, injury, or disease. Since arginine is a precursor of nitric oxide (NO), any deficiency of arginine can limit the production of NO (Cooke, et al., 1997).

It has been shown that NO predominantly acts as an inducer of apoptosis in breast cancer cells. Apoptotic agents, such as phorbol esters and tumor necrosis factor-alpha and peptide hormones, have been shown to increase NO production in breast cancer cells. The production of NO was directly correlated with the degree of apoptosis in these cells (Simeone, et al., 2002).

The role NO plays in the apoptosis of cancer cells was further confirmed in nude mice xenografts of head and neck cancer cells (Kawakami, et al., 2004). Our in vitro studies with A2058 melanoma cells have shown that arginine can act synergistically with lysine in reducing their Matrigel invasion (Netke, et al., 2003).

Nutrient Combinations in Cancer Therapy

1. Scientific Rationale on the Novel Approach of Nutrient Synergy in Cancer Therapy

Thus, over past decades, many approaches to cancer control through the therapeutic use of micronutrients have been presented. These approaches, however, did not lead to a breakthrough in the effective control of cancer because the understanding and selection of the therapeutic targets of the individual nutrients investigated were incomplete.

A major step in this direction was the landmark publication by Rath, et al. (1992), which for the first time drew attention away from the origin of individual cancers and the application of individual nutrients. The novel approach presented in this publication focuses on the common pathomechanism of all cancers – the destruction of the extracellular matrix as a precondition for cancer growth and metastasis and its inhibition by natural means.

ECM plays a very important role in the body as a stability factor and a communication milieu for various growth factors, cytokines, and intercellular signal transduction. Faulty formation of ECM can lead to several chronic conditions, such as arthritis, atherosclerosis, cancer and others. Cancer cells have to break through the ECM to spread locally (increase in tumor size) and infiltrate other parts of the body (metastasis). Metastasis involves the adhesion of cancer cells to the ECM and secretion of enzymes called matrix metalloproteinases (MMPs), which dissolve the ECM and allow the migration of malignant cells through the matrix. These cells pass through the walls of blood vessels and spread to other parts of the body. Constituents of the ECM include collagen fibers, elastin fibers, various glycoproteins, proteoglycans and other components.

The major barrier in the basement membrane and ECM is collagen. Collagen fibers are triple helical chains of amino acids held firmly together. The firm bonding of collagen fibers is achieved through hydrogen bonds formed between different chains of collagen fibrils and by hydroxylation of proline and lysine molecules in the collagen chains. While the amino acids proline and lysine are required for the formation of collagen chains, ascorbic acid is essential for the hydroxylation reaction. Therefore, it becomes necessary to provide adequate amounts of proline, lysine, and ascorbic acid in the diet for the formation of healthy and strong ECM.

The novel approach to the control of cancer by nutrient synergy presented by Rath, et al. (1992) can be summarized as follows:

1. All cancer cells spread by using the same pathomechanism, the production/activation of proteolytic enzymes that digest the extracellular matrix. The most widely used mechanism, however, is the activation of plasminogen through the 10 to 100-fold increase in the secretion of plasminogen activator as a result of the malignant transformation of cells. Active plasmin, in turn, triggers the activation of metalloproteinases (MMPs), collagenases, and other proteolytic enzymes, leading to the degradation of basement membranes and the extracellular

matrix. The aggressiveness and malignancy of any type of cancer is determined by the rate of matrix degradation triggered by cancer cells.

2. By its capability to inhibit plasmin activation, the natural amino acid lysine, as well as synthetic lysine analogues, is able to mitigate or block tissue degradation and, consequently, curb cancer growth and metastasis. In fact, lysine can inhibit most MMPs by interfering with the tissue plasminogen activator and, consequently, the conversion of plasminogen to plasmin, an essential enzyme in the MMP activation cascade. Through this mechanism, lysine can help decrease the break down of collagen fibers in ECM, basement membranes, and blood vessels walls, thereby reducing the metastatic ability of cancer cells (Rath, et al., 1992; Sun, et al., 2002).
3. The therapeutic synergy of the amino acid lysine with vitamin C is particularly desirable; while lysine can inhibit the degradation of ECM, vitamin C, in combination with other micronutrients, increases the stability of the connective tissue by optimizing the production of collagen and other matrix components. The main therapeutic targets of the combined administration of lysine and vitamin C are tumor encapsulation and the prevention of metastases.

Based on these discoveries, Rath, et al. proposed that all types of cancer could be controlled by optimum — i.e., therapeutic — dosages of certain essential nutrients. This far reaching conclusion is corroborated by established clinical findings.

A low plasma concentration of ascorbic acid is characteristic for cancer patients (Anthony, et al., 1982; Nunez, et al., 1995; Kurbacher, et al., 1996; Gackowski, et al., 2002). This may be attributed to the decrease in the dietary intake of ascorbic acid caused by the inanition seen in cancer patients, as well as the increased demands for ascorbic acid incidental to the excessive breakdown of ECM.

Lysine is an essential amino acid, as the body cannot synthesize it. The decreased food intake of cancer patients, and especially those on low protein diets, will surely result in a deficiency of this nutrient.

Proline is normally synthesized in the body, but the hydroxyproline content of tumor tissue is low (Chubinskaia, et al., 1989). Hydroxyproline excreted in the urine of cancer patients is also higher than that found in healthy persons or non-cancer patients (Okazaki, et al., 1992). These observations suggest the increased breakdown of ECM in cancer tissues. It is very likely that proline synthesis in the body cannot keep up with this extra demand, leading to a conditioned deficiency of proline and a subsequent reduction in collagen fiber formation.

These deficiencies result in the formation of weak ECM, which facilitates the breakdown of the ECM structure by cancer cells. Adequate intake of these nutrients by cancer patients would, therefore, be beneficial in preventing metastasis. In our studies on Matrigel invasion by cancer cells, we observed that the addition of lysine, proline, and ascorbic acid to cell culture media at concentrations approximating those found in the blood of healthy individuals inhibited the migration of cancer cells through the Matrigel membrane by 50%, 10%, and 30% in breast cancer cells (MDA-MB-231), melanoma cells (A2058), and colon cancer cells (HCT116), respectively (Netke, et al., 2003).

2. Nutrient Synergy: Vitamin C, Lysine, Proline, EGCG, Arginine, N-Acetyl Cysteine, Selenium, Copper and Manganese

Studies at the Dr. Rath Research Institute of Cellular Medicine in California have shown that nutrients can work synergistically with EGCG (Netke, et al., 2003). We have found that a combination of ascorbic acid, lysine, and proline used with EGCG enhanced the anti-invasion activity of 20 µg/ml of EGCG to that of 50 µg/ml EGCG when used alone. A review of literature as detailed above has indicated that several other nutrients exhibit anti-cancer activities. However, this possible synergistic interaction between several nutrients has not been investigated. Based on the evidence available in the literature and our own research, we hypothesized that a combination of ascorbic acid, lysine, proline, green tea extract, arginine, N-acetyl cysteine, selenium, copper and manganese should work synergistically. This particular combination was designated NS (Table 1).

Table 1. Concentrations of various components in NS used at 1,000 µg/ml

Components of NS	Concentration of Nutrients in 1,000 µg/ml Solution
Ascorbate	900 µM
Lysine	1,100 µM
Proline	1,100 µM
Arginine	500 µM
N-Acetyl Cysteine	250 µM
EGCG	150 µM
Selenium	85 µM
Copper	7 µM
Manganese	4 µM

The hypothesis was verified both in tissue culture studies and laboratory animal studies. Incorporating just 10 µg/ml of this nutrient combination (NS) reduced the Matrigel invasion of melanoma cells A2058 and breast cancer cells MDA-MB-231 to 20% and 53%, respectively. When used alone, 20 µg/ml of EGCG reduced the number of MDA-MB-231 cells migrating through Matrigel to about 70% (Netke, et al., 2003), while a quantity as small as 0.8 µg/ml of EGCG in NS reduced the number of migrating cells to 53% (Roomi, et al., 2003). Thus, by including nutrients such as N-acetyl cysteine, arginine, selenium, manganese and copper, in addition to ascorbic acid, proline, lysine and green tea extract, we could obtain a reduction in cell invasion at a much lower concentration of EGCG than when using EGCG alone.

NS was found to be effective in a variety of cancer cell types, including solid tumors and the cells involved in leukemia and HTLV-1 virus-derived leukemia ATL (Roomi, et al., 2004 a, b, c, d, e, f, g and Harakeh, et al., 2004 a, b). We have also investigated the requirement of NS for complete inhibition (100%) of Matrigel invasion for several cell lines. It was observed that the cells differed in their response to NS (Table 2).

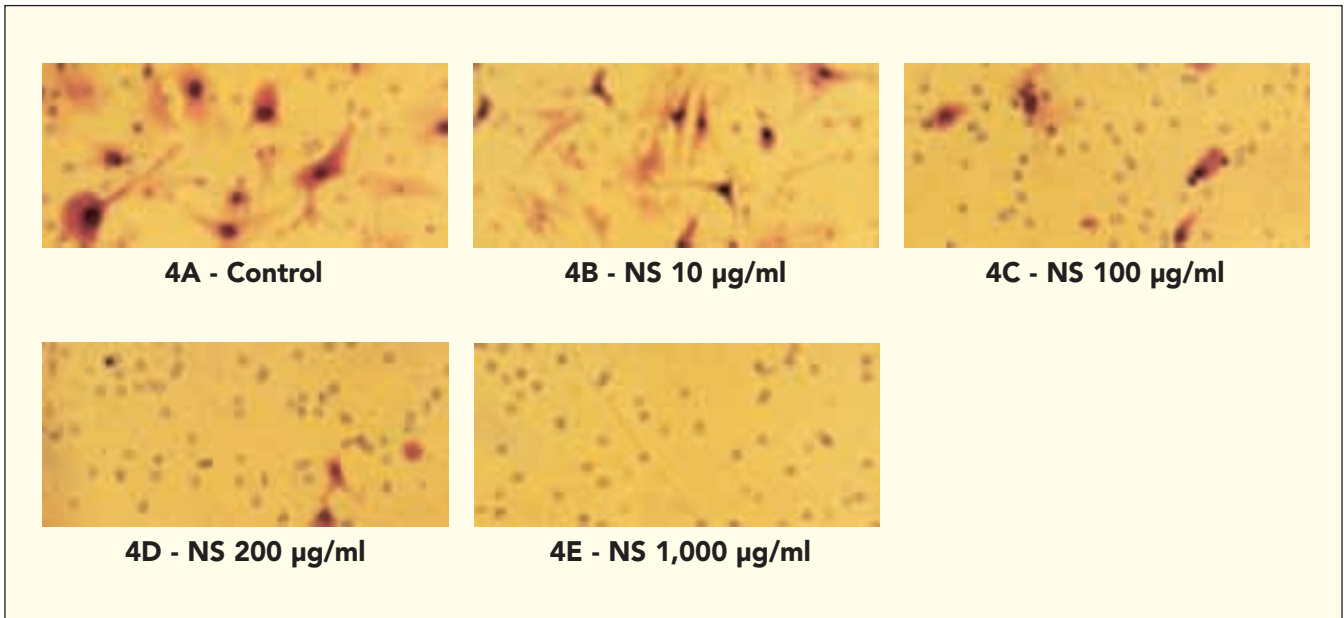


Figure 2: Nutrient synergy (NS) inhibited Matrigel invasion of human fibrosarcoma HT1080 cells by 100% at 1,000 µg/ml.

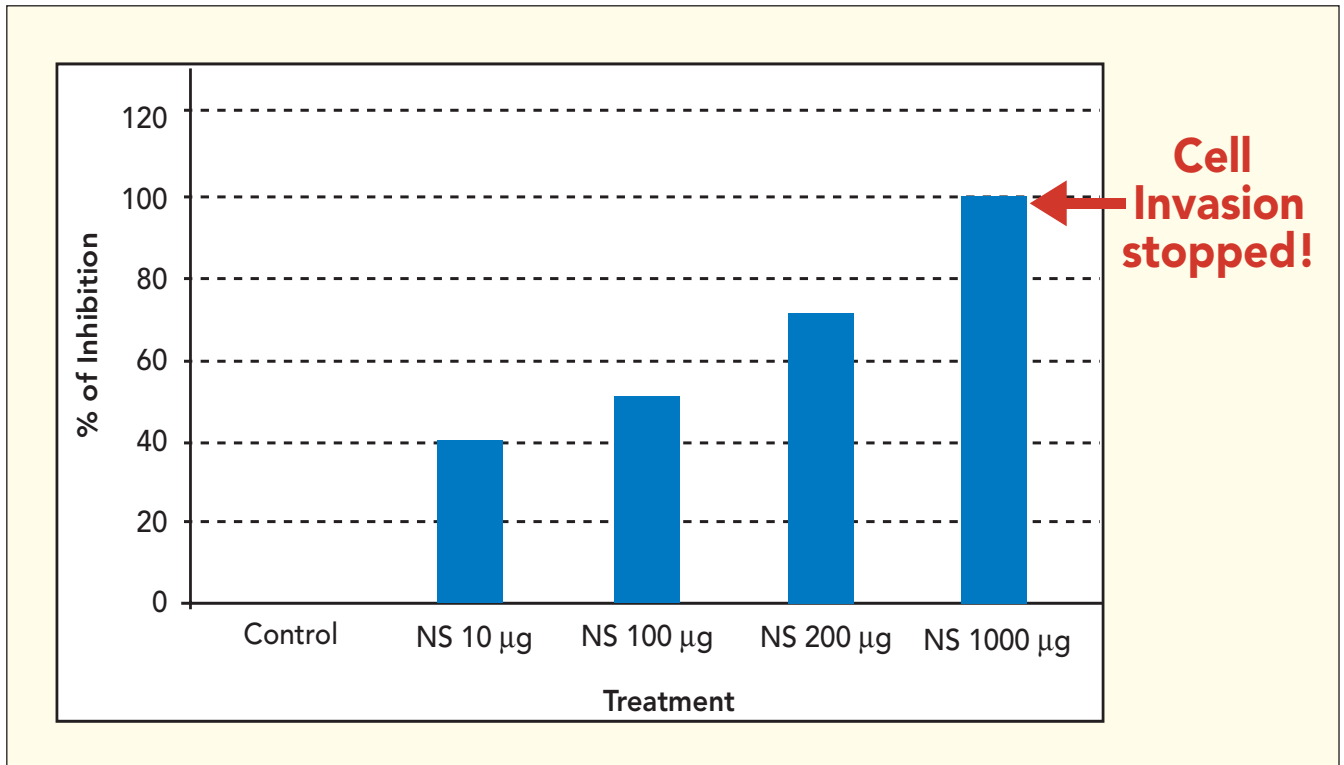


Table 2.

Cancer Cell Origin	Amount of NS Needed for 100% Inhibition of ECM Invasion
Breast (MDA-MB-231)	100 µg/ml
Breast (MCF-7 + Estradiol)	100 µg/ml
Osteosarcoma (MNNG/U2OS)	100 µg/ml
Cervical Cancer (CCL2)	500 µg/ml
Lung Carcinoma (A-548)	500 µg/ml
Pancreas (MIA PACA-2)	500 µg/ml
Prostate (LNCaP)	500 µg/ml
Testis (NT2/DT)	500 µg/ml
Colon (HCT116)	500 µg/ml
Bladder Cancer (T-24)	1,000 µg/ml
Cervical Cancer (DoTc2451)	1,000 µg/ml
Fibrosarcoma (HT1080)	1,000 µg/ml
Ovarian Cancer (SKOV-3)	1,000 µg/ml
Prostate (PC-3)	1,000 µg/ml
Renal Carcinoma (786-0)	1,000 µg/ml
Synovial Carcinoma	1,000 µg/ml

This inhibition of the invasive properties of cancer cells was accompanied by the inhibition of MMP-9 and MMP-2 activity (enzymes involved in cancer spread and metastasis) (Figure 3).

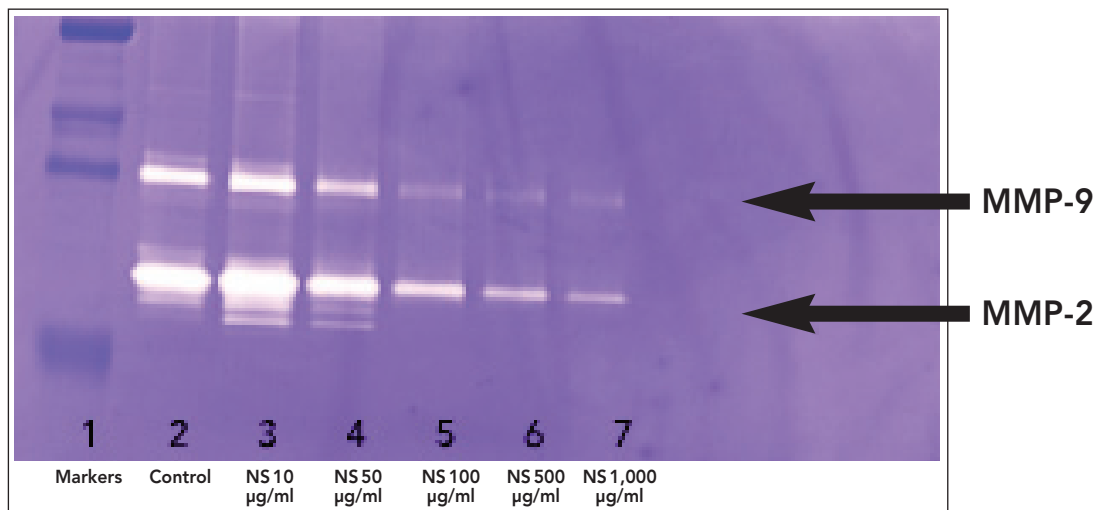


Figure 3: Human fibrosarcoma HT1080 cells demonstrated expression of MMP-2 greater than MMP-9, both of which were inhibited by the nutrient mixture (NS) in a dose-dependent fashion with virtual total inhibition of MMP-9 at 100 µg/ml and nearly total inhibition of MMP-2 at 1,000 µg/ml.

In addition, NS was effective in decreasing the secretion of vascular endothelial growth factor (VEGF) both in control and PMA-stimulated cells such as osteosarcoma U2OS (a decrease of 70% and 100%, respectively), fibrosarcoma, and other cancer cell types. This factor has been implicated in the promotion of new blood vessel formation (angiogenesis) in tumors. The anti-angiogenic potential of NS was also demonstrated by its effect on lowering the secretion of angiopoietin by 93%.

Moreover, NS decreased endothelial cell migration by 62% (Figure 4), which is the essential step in the formation of blood vessel tubules. The anti-angiogenic effects of NS were confirmed with *in vivo* models, such as the chick embryo angiogenic model, where NS reduced the mean number of new blood vessel branches from 22 to 10 (Roomi, et al., 2004).

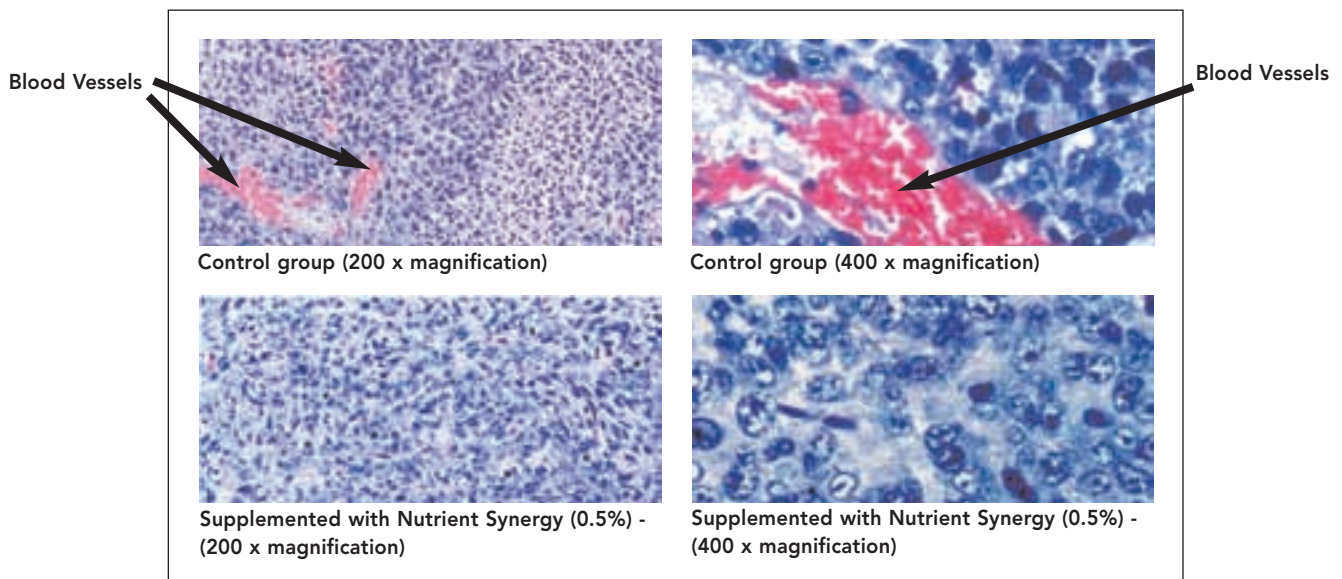


Figure 4: Nutrient synergy inhibits formation of new blood vessel in osteosarcoma U2OS tumors induced in mice.

NS decreased the proliferation of various types of cancer cells in a concentration-dependent fashion, including blood cancers (leukemias) and hormone-dependent cancers such as breast and prostate cancers. The pro-apoptotic effect of NS on cancer cells was indicated by the upregulation of p53, p21, and Bax protein expression and the decreasing of Bcl-2a, as well as cell cycle arrest measured by cell flow cytometry, the upregulation of TGF-beta, and the decreasing of TGF-alpha cytokine expression (Harakeh, et al., 2004).

Xenograft studies conducted in nude mice fed standard diets and diets enriched with 0.5% NS showed a reduced growth of tumors: breast cancer (MDA-MB-231) by 27%, prostate cancer (PC-3) by 53%, colon cancer (HCT116) by 63%, osteosarcoma (MNNG) by 53%, neuroblastoma by 25%, fibrosarcoma (HT1080) by 50% (see Figure 5) and melanoma (A2058) by 57% after four weeks on NS-supplemented diets compared to controls. The histology of tumors revealed a decreased mitotic index (Ki67), decreased staining for VEGF and MMP-9 (critical for metastasis and angiogenesis), and changes in fibronectin with NS supplementation (Roomi, et al., 2004) (Figure 6).

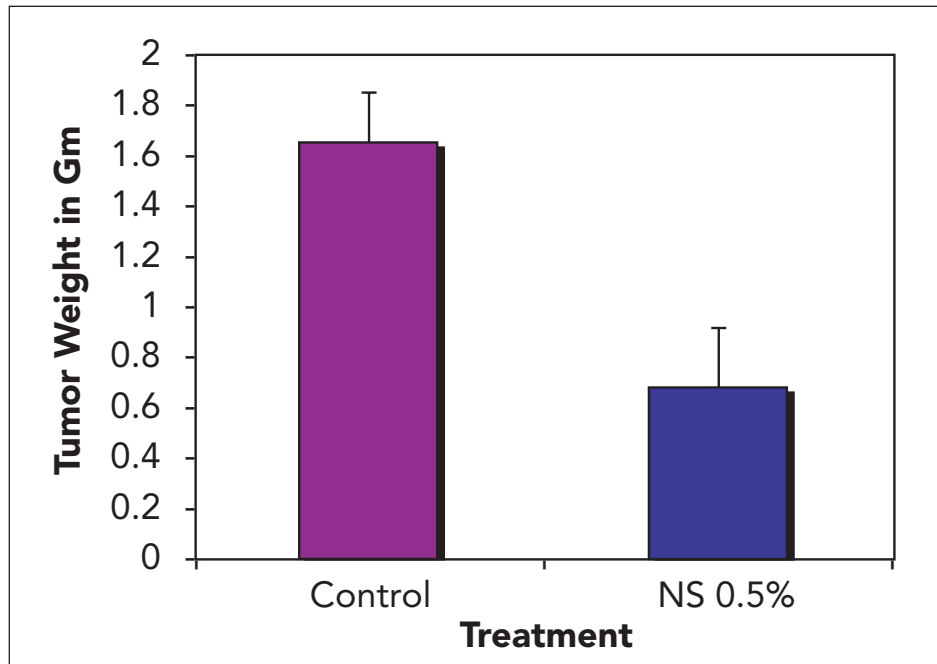


Figure 5: Human fibrosarcoma HT1080 xenografts in male nude mice. The nutrient supplemented nude mice (NS 0.5%) developed significantly smaller tumors (by 59%, $p=0.0001$) and less vascular ones than the control group of nude mice.

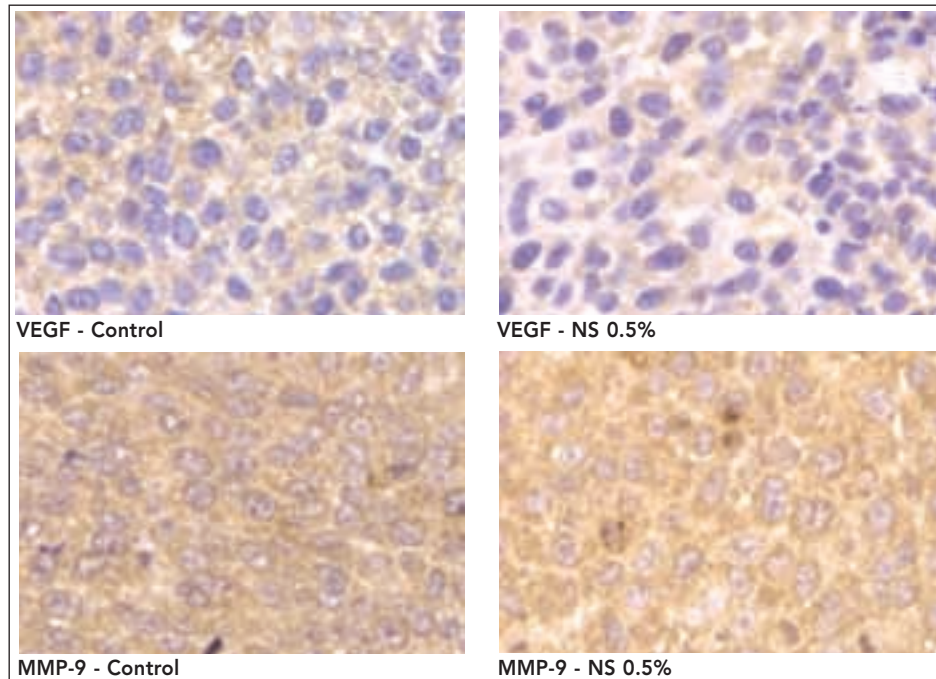


Figure 6: Immunohistochemistry of human fibrosarcoma HT1080 xenografts in male nude mice. The tumor tissue in the control group showed greater staining for VEGF and MMP-9 than the supplemented group. Greater staining represents higher secretion levels.

NS was also effective in decreasing the development of chemically induced (N-methyl-nitrosourea) tumors in female rats. After two weeks of exposure to N-methyl-nitrosourea, the animals were divided into two groups: one continued receiving a standard diet and the other received a standard diet supplemented with 0.5% NS. After four weeks, tumors developed in 90% of animals on the control diet; while on the NS diet, 50% of the female rats were tumor-free (Figure 7). Moreover, total tumor weight in the NS-fed group was reduced by 78%, tumor burden was reduced by 60.5%, and the number of large tumors was six compared to 19 in the control group (Roomi, et al., 2004).

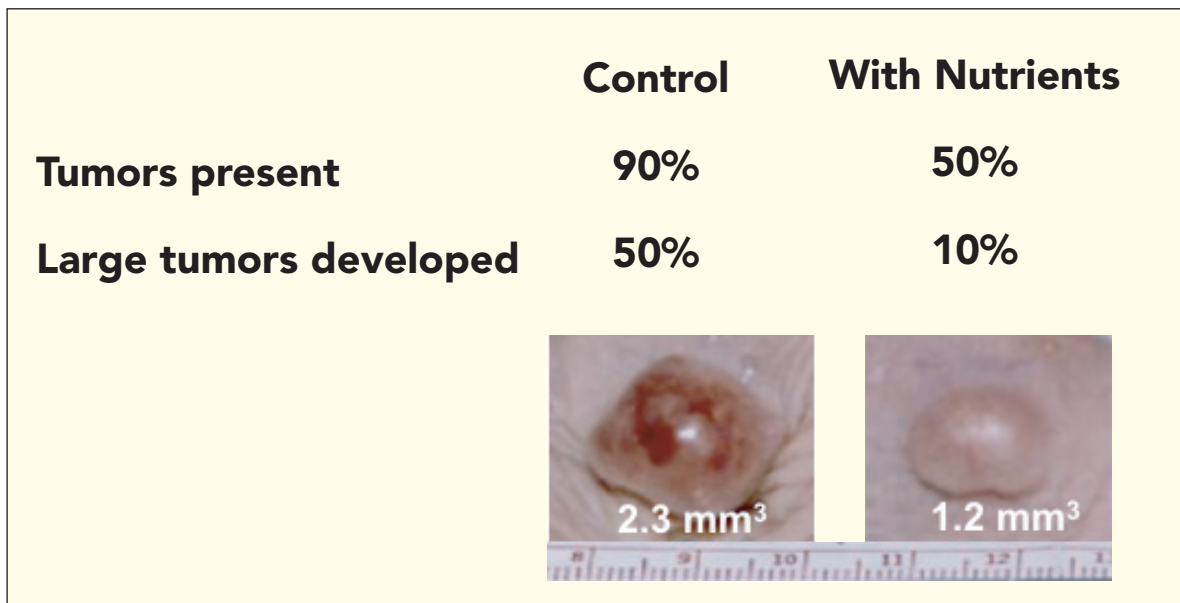


Figure 7: Cellular nutrients can reduce the size of toxin-induced breast cancers.

Several in vitro and in vivo studies clearly support the high therapeutic potential of NS because of its favorable effects on multiple biochemical processes involved in metastasis, angiogenesis, apoptosis and inflammation. The above review also shows that the potential is applicable to a wide variety of cancer types.

3. Other Nutrient Combinations

The combination of ascorbic acid and sodium selenite induced re-differentiation of gastric cancer cells and inhibited cell growth by enhancing the activities of anti-oxidative enzymes and inducing the formation of H_2O_2 (Zheng, et al., 2002).

In cell culture studies, it was found that individually 50 $\mu\text{g}/\text{ml}$ of vitamin C, 10 $\mu\text{g}/\text{ml}$ of poplar carotenoids, 10 μg of alpha-tocopherol succinate and 7.5 $\mu\text{g}/\text{ml}$ of retinoic acid had no effect on the growth of melanoma cells. However, the combination of the four reduced the cell number by 56%. When the level of ascorbic acid was raised to 100 $\mu\text{g}/\text{ml}$, the cell number was further reduced by 13% (Prasad, et al., 1994).

Nutrients as Adjuncts to Standard Cancer Therapy

1. Essential Nutrients Used with Chemotherapy or Radiation Therapy

There is enough experimental evidence to show that nutrient therapy used with conventional therapy can exert synergistic activity. It can also protect against the adverse effects of chemotherapy.

- *Cisplatin with Selenium and Vitamin C*

The genotoxicity of anti-cancer drugs is one of their most serious side effects, due to the possibility of inducing new malignancies. Cisplatin (Cis-diammine dichloro platinum) is a potent anti-cancer drug widely used in clinical practice. It, however, displays several severe side effects among which nephrotoxicity and genotoxicity are the most serious (Ferguson and Pearson, 1996).

Recently, Cisplatin has been combined with selenium, as this nutrient has been found to protect against nephrotoxicity. However, it was shown that this conjugate still damages DNA (Blasiak, et al., 1999). Vitamin C, at concentrations as low as 10 μM and 50 μM (readily achievable in human plasma), has been reported to diminish the DNA damage evoked by the Cisplatin selenium conjugate (Blasiak and Kowalik, 2001). Selenium supplementation can also prevent the induction of resistance to Cisplatin in ovarian tumors (Caffrey and Frenkel, 2000).

- *Cisplatin with Vitamin C and Vitamin E*

In studies with transgenic mice bearing lung carcinoma, the administration of high doses of ascorbic acid and vitamin E along with Cisplatin induced a significantly lower rate of cancer growth and reduced the metastatic load. Cisplatin, combined with soybean oil and vitamin E in high doses (40 mg/kg), did not show significant therapeutic value (Yam, et al., 2001).

- *Cisplatin, Tamoxifen and Dicarbazine with Vitamin C, Vitamin E, Beta-Carotene and Retinoic Acid*

In cell culture studies with melanoma cells (Prasad, et al., 1994), it was reported that the use of Cisplatin (1 $\mu\text{g}/\text{ml}$) inhibited cell multiplication by approximately 33%. When Cisplatin was combined with the antioxidant mixture, inhibition was raised to 62%. The same trend was seen when the antioxidant mixture was used with Tamoxifen (19% vs. 70%) and dicarbazine (29% vs. 62%). The tested antioxidant mixture contained vitamin C (50 $\mu\text{g}/\text{ml}$), alpha-tocopheryl succinate (10 $\mu\text{g}/\text{ml}$), beta-carotene (10 $\mu\text{g}/\text{ml}$) and 13-cis-retinoic acid (7.5 $\mu\text{g}/\text{ml}$).

- *Irradiation with Vitamin A and Beta-Carotene*

Seifter, et al. (1984) investigated the effects of irradiation alone and co-administered with vitamin A and beta-

carotene in mice with transplanted adenocarcinoma. When irradiation was given alone, the one-year survival rate was zero out of 24 rats. The survival rate remained the same when designated amounts of vitamin A and beta-carotene were given separately. However, when irradiation was combined with vitamin A or beta-carotene, the survival rate increased to 22 out of 24 rats in both combinations. Antioxidant (vitamins A, C, and E) reduction of tissue toxicity induced in nude mice by radio-immunotherapy was observed by Blumenthal, et al. (2000).

- *Doxorubicin and Vitamin E*

The incorporation of doxorubicin (0.1 µg/ml) and vitamin E as alpha-tocopheryl succinate (10 µg/ml) separately did not affect the cell multiplication of Hela cells. However, when both agents were combined, cell multiplication was inhibited by 80% (Prasad, 2003).

- *Doxorubicin and N-Acetyl Cysteine*

N-acetyl cysteine, when administered with doxorubicin, synergistically reduced lung metastasis in nude mice (Morini, et al., 1999).

- *Cyclophosphamide, Methotrexate, and 5-Fluorouracil with Vitamin C*

The combined administration of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) is routinely used in treating breast cancer. This treatment, however, instigates lipid abnormalities. Administration of ascorbic acid (200 mg/kg bw) along with cyclophosphamide (10 mg/kg bw), methotrexate (1 mg/kg bw), and 5-fluorouracil (10 mg/kg bw) to fibrosarcoma-bearing rats lowered the levels of total cholesterol, triglycerides, very low-density lipoproteins and low-density lipoprotein cholesterol (Murlikrishnan, et al., 2001).

- *Sulindac and Green Tea Extract*

Use of green tea extract with Sulindac in multiple intestinal neoplasia in mice significantly reduced the number of intestinal tumors by 44.3% and 49% over the reduction obtained separately with green tea extract and Sulindac (Suganama, et al., 2001).

These results clearly indicate that a combination of one or more nutrients, along with standard therapy, can help intensify cancer treatment and protect healthy cells and organs.

2. Combination of Multiple Antioxidants with Chemotherapy

The effects of vitamins and nutrients in combination with irradiation or chemotherapy have not been extensively evaluated in patients in a systematic manner, due mostly to the lack of funds to support such trials. However, available studies reveal the benefits of this approach in the management of cancer. Trials in patients with small-cell and non-small cell lung cancer on multiple antioxidant treatment with chemotherapy and/or irradiation showed a

markedly enhanced median survival time and tolerance to the treatment (Jaakkola, et al., 1992; Prasad, et al., 2001).

The examples of various nutritional protocols used with standard therapies in cancer are briefly outlined below:

- Beta-Carotene, 10,000 - 20,000 IU; Alpha-Tocopherol, 300-800 IU; Ascorbic Acid, 2,000 - 4,000 mg; Selenium, 865 ug; Multivitamins and Fatty Acids with Standard Therapy

Jaakkola, et al. (1992) used this combination along with conventional therapy in patients with small cell lung cancer. There were 18 patients in the study, and the median survival time for the whole group was 505 days. Fourteen patients survived for more than 12 months and six patients survived for more than 24 months. One patient survived more than five years. Eight patients were still alive with a mean survival time of 32 months at the end of the study. They also observed that the patients receiving the supplements were better able to tolerate the chemotherapy and radiation treatments. The patients that survived were put on the supplements earlier in the course of the disease. The treatment prolonged the survival time of the patients compared to historical records.

- Vitamin A, 40,000 IU; Vitamin B6, 100 mg; Vitamin C, 2,000 mg; Vitamin E, 400 IU; Zinc, 90 mg

In a study in 65 bladder cancer patients (Lamm, 1994), the effects of various vitamins used at RDA allowance levels were compared with higher doses of various vitamins combined with these nutrients at RDA levels. The composition of higher dose supplements is indicated above. The overall recurrence of the tumor after 10 months was observed in 24 out of 30 (80%) patients in the RDA arm and 14 out of 35 (40%) patients in the higher dose arm. The five-year estimates of tumor recurrence were 91% in the RDA arm and 41% in the higher dose arm ($p=0.0014$, Mantel-Cox).

- Vitamin C, 2,850 mg; Vitamin E, 2,500 IU; Beta-Carotene, 32.5 IU; Selenium, 387 µg and Other Nutrients with Standard Therapy

Lockwood, et al. (1994) used the above combination, in addition to secondary vitamins, minerals, essential fatty acids (1.2 gm gamma linolenic acid and 3.5 gm n-3 fatty acids) and coenzyme Q10 (90 mg/d), to treat 32 breast cancer patients. This was termed an Adjuvant Nutritional Intervention in Cancer Protocol (ANICA Protocol). The nutritional protocol was added to the surgical therapeutic treatment of breast cancer. None of the patients died (the expected number of deaths was four), none of the patients showed signs of further distant metastasis, quality of life improved (no weight loss, reduced use of pain killers) and six patients showed apparent partial remission.

- Antioxidant and Mineral Mixture (Vitamin C, 6,100 mg; Alpha-Tocopherol, 1,050 mg;

Beta-Carotene, 60 mg; Selenium, 900 µg) with Standard Chemotherapy

In randomized clinical studies, Pathak, et al. (2002) used a high-dose multiple antioxidant mixture (see above) along with copper sulphate, 6 mg; manganese sulphate, 9 mg; and zinc sulphate, 45 mg as an adjunct to chemotherapy. There were 29 patients in the chemotherapy arm against 22 in the chemotherapy plus antioxidant arm. The results of the study are presented in Table 3. It can be seen that the addition of antioxidants to the chemotherapy protocol improved the performance of the patients in all the parameters measured.

Table 3. Preliminary results of a randomized clinical trial using high-dose multiple antioxidants as an adjunct to chemotherapy (Pathak, et al., 2002)

Treatment and Tumor Response	Chemotherapy Arm (29 patients)	Chemotherapy + Antioxidants Arm (22 patients)
Number of patients completing six cycles	11	16
Complete response	0	1
Partial response	9	16
Progressive disease	15	8
Overall survival over one year	7	14

- Vitamin C (as calcium ascorbate), 8 g; Vitamin E as Alpha-Tocopherol Succinate, 800 IU; Natural Beta-Carotene, 60 mg with Radiation

A randomized pilot trial (Phase I/II) using the above mixture divided in two doses in patients with Stage 0-III breast cancer receiving radiation has been recently completed in the U.S. (Walker, et al., 2002). In these studies, 25 patients were given radiation only, while 22 patients received radiation plus vitamin supplements. During the follow-up period of 22 months in which no supplements were given, two patients in the radiation arm developed new cancers. None of the patients in the combination arm (22 patients) developed new cancers. Thus, there is enough evidence to show that the use of antioxidants, along with conventional treatment, helps patients.

3. Reasons for Discrepancies in Obtaining Beneficial Therapeutic Effects of a Combination of Antioxidants with Standard Therapies

The review that is often cited in this context is that of Ladas, et al. (2004). The investigators here reviewed 31 observational studies and 21 intervention studies of cancer patients published in English journals. These stud-

ies varied in study design, timing of observation/intervention, intervention protocol, malignancy and anti-cancer regimen and doses of antioxidants used. The investigators concluded that these "inconsistencies preclude a definite conclusion as to the effect of chemotherapy on the antioxidant status in the patients."

In spite of the experimental and clinical evidence cited here, an impression has been nurtured in the medical community that the use of antioxidants in higher doses does not help cancer patients and, therefore, such use should not be recommended. Prompted by such a dichotomy of views, Prasad, et al. (2001) critically scrutinized various relevant studies that might have led to the negative view. They concluded that the negative view arose because of the following factors:

- A. The effects of most of the vitamins and micronutrients obtained at low levels of supplementation are extrapolated to project the effects of higher doses.
- B. The results obtained with a single antioxidant are considered to be no different from those obtained when that antioxidant forms only a component of the mixture of multiple antioxidant nutrients.
- C. The effects of antioxidants obtainable with cancer cells are projected from those obtained with normal cells.
- D. The effects of prolonged exposure to vitamins are considered to be the same as those obtained with short duration exposure.

It would appear from the above that a combination of antioxidants in high doses benefits patients.

4. Combinations of Higher Doses of Antioxidants Recommended by Various Research Groups for Use in Conjunction with Conventional Anti-Cancer Therapy

A convention of medical practitioners, epidemiologists, nutritionists and other scientists held at the Bristol Cancer Help Center formulated a consensus statement regarding nutritional guidelines for cancer patients (Goodman, Howard, and Barker, 1994). While recommending a mixture of nutrients, they made it clear that they were not aware of any reasons for stopping vitamin C supplementation during radiation and chemotherapy.

They recommended nutrient supplements for individuals in both the active and maintenance stages of cancer treatment (Table 4).

Table 4. Suggested daily supplement levels for cancer patients (Goodman, Howard, and Barker, 1994)

Nutrient	Active Cancer	Maintenance Level
Vitamin A	10,000 IU	7,500 IU
Beta-Carotene	25,000 IU	10,000 IU
Vitamin B Complex	50 mg	50 mg
Vitamin C	6-10 g	1-3 g
Vitamin E	200-400 IU	100 IU
Zinc (elemental)	15-25 mg	15 mg
Selenium	200 mcg	100 mcg
Chromium GTF	100 mcg	50 mcg
Magnesium	100-200 mg	100-200 mg

A group of researchers at the School of Medicine at the University of Colorado and the Department of Pathology at the University of California, San Francisco reviewed the experimental evidence available with respect to the use of antioxidants in the treatment regimen of cancer patients (Prasad, et al., 2001). Based on the review and their own studies, Prasad (2003) recommended a mixture of antioxidants for use in cancer patients (Table 5).

Table 5. Mixture of antioxidants recommended by Prasad (2003)

Nutrient	Active Treatment Protocol	Maintenance Protocol
	Nutrient Mixture*	Nutrient Mixture*
Vitamin C	8 g	4 g
Vitamin E	800 IU	400 IU
Natural Beta-Carotene	60 mg	30 mg

*Nutrient mixture contains multiple micronutrients, including the vitamins A, C, and E and natural beta-carotene, vitamins D and B, and appropriate minerals.

The new nutrient synergy approach to cancer control developed by Rath and his research group is not limited to antioxidants, but seeks to take advantage of the synergetic effect of several nutrients that have individually proven their efficacy against various therapeutic targets in the control of cancer. The benefits of the proposed nutrient combinations (Table 6) have been identified by their own laboratory research and by numerous cases of testimonial evidence.

Due to the fact that the mechanisms of action of this nutrient synergy at the cellular level have been identified, this new therapeutic approach has been named "Cellular Medicine." The Cellular Medicine recommendations as provided in Table 6 can be applied in cancer. The formulation is to be used along with the nutrient support of a basic multivitamin, minerals, and essential nutrients as a necessary measure to correct the nutrient deficiencies and metabolic imbalances caused by pathological conditions.

Table 6. Cellular Medicine nutrients in cancer (Rath and Associates)

Nutrient	Cancer Metabolic Correction (Low Ranges)	Cancer Metabolic Intervention (High Ranges)
Vitamin C	350 - 700 mg	5 > 10 g
Lysine	500 - 1,000 mg	2,000 - 5,000 mg
Proline	375 - 750 mg	1,500 - 4,000 mg
Arginine	250 - 500 mg	1,000 - 2,000 mg
N-Acetyl Cysteine	100 - 200 mg	400 - 1,000 mg
Green Tea Extract	500 - 1,000 mg	2,000 - 4,000 mg

Selenium	15 - 30 mcg	60 - 120 mcg
Copper	1 - 2 mg	4 mg
Manganese	0.5 - 1 mg	2 - 4 mg

Most Frequent Concerns of Oncologists Regarding Antioxidant Use in Cancer Therapy

Some oncologists are concerned about the use of antioxidants during cancer treatment. Major concerns originate from some published reports that have been interpreted to show an unfavorable impact of antioxidants on the incidence and treatment of cancer. A perusal of these reports is warranted to obtain a realistic perspective on the role of antioxidants as adjuncts to conventional therapy or as an alternate therapy. Some of these concerns are discussed below.

1. Uncertainty About the Long-Term Effects of Combining Chemotherapy Drugs with Antioxidants

A publication from the Northwest Natural Health Specialty Care Clinic in Seattle, Washington (USA) reported, "No definitive studies have demonstrated the long-term effects of combining chemotherapeutic agents and oral antioxidants in humans." (Labriola and Livingston, 1999) It is disconcerting to realize that these researchers did not consider the reports of Jaakkola, et al. (1992); Lockwood, et al. (1994); and Lamm, et al. (1994). In all these studies, the patients benefited from the use of antioxidants. Several papers published since that time (Prasad, et al., 1999; Pathak, et al., 2002; Walker, et al., 2002; Prasad, 2003) indicate that combining antioxidants with conventional therapy improves the recovery of cancer patients.

A recent review of several clinical trials conducted in cancer patients by Dr. Kelly and his group in the Pediatric Oncology Department at Columbia University, USA (Ladas, et al., 2004) provide the details of various supplements used in cancer treatments. The authors reviewed 52 trials, which varied in study design, timing of observation/intervention, intervention protocol, malignancy and anti-cancer regimen. This review covered 31 "clinical" trials in which antioxidants were given in conjunction with conventional therapy. Only three of these studies used a combination of large doses of antioxidants (Jaakkola, et al., 1992; Lockwood, et al., 1994; Lamm, et al., 1994). In all three studies, the patients benefited from the use of antioxidants.

Thus, there is enough evidence in the literature to establish convincingly that cancer patients stand to benefit when a combination of megadoses of multiple antioxidants are used along with conventional therapy. There does not seem to be any uncertainty about the benefits.

2. Antioxidants and Cancer Risk

The impression that antioxidants can promote cancer is based on two human studies. In one study, investigators used 25 or 30 mg of beta-carotene with 25,000 units of vitamin A in the treatment group and a placebo in the control group. One of the criteria for admission into the studies was that the person must have been already exposed to the risk of developing lung cancer because of their smoking habits or inhaling asbestos dust. The studies covered a period of approximately two years.

At the end of the study period, the number of persons that developed lung cancer was 5.92 and 4.62 in the treatment and placebo groups, respectively. The investigators concluded that "the combination of beta-carotene and vitamin A may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer." (Omenn, et al., 1996) The researchers also stated in this paper, "We could find no support for the hypothesis that subjects with the highest serum levels of beta-carotene were at greater risk for lung cancer." The authors further indicated, "It is possible that the excess mortality in the active treatment group may have vanished or become statistically insignificant with the completion of the intended intervention period plus several years of follow-up."

There are several points that deserve our attention here:

- The findings relate to the use of vitamin A and a synthetic beta-carotene and, therefore, cannot be extrapolated to all antioxidants.
- All participants in the study had already been exposed to the risk of lung cancer either because of their smoking habits or because they had been exposed to asbestos dust. The findings are, therefore, logically applicable only to smokers and persons exposed to asbestos dust.
- More importantly, the incidence of cancer could not be related to the serum levels of beta-carotene.
- The authors clearly state that the difference between the treatment and the control group could have disappeared had the trial been run for the intended period, plus several years of follow-up.

In a similar study (Albanese, et al., 1995), a group of smokers received beta-carotene (25 mg) and alpha-tocopherol (50 mg) in a 2x2 factorial design. They reported that persons taking beta-carotene only had a higher incidence of cancer at several sites, notably the lung, prostate, and stomach. The persons that received alpha-tocopherol alone had a lower incidence of prostate and colorectal cancer, but a higher incidence of stomach cancer than those who did not receive alpha-tocopherol. The population with the higher baseline serum level of dietary beta-carotene and alpha-tocopherol had a lower incidence of lung cancer. It is worth noting that the level of alpha-tocopherol used in these studies was very low. It is intriguing that the population with higher baseline serum levels of dietary beta-carotene and alpha-tocopherol had a lesser incidence of lung cancer. As in the previous study, the experimental subjects in this study were smokers only.

Here again, the doses of vitamins used were low; however, there was an inverse relationship between serum levels of beta-carotene and vitamin E and the incidence of lung cancer. There are other studies that have been

conducted in both smokers and non-smokers.

The relation between dietary intake of vitamins C, E, and A and lung cancer was examined in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study of 3,698 men and 6,100 women, aged 25-74 years. The median period of follow-up was 19 years. For vitamin A consumed from fruits and vegetables (carotenoids) by current smokers, the relative risk of lung cancer in the highest quartile compared with those in the lowest quartile was 0.49. The incidence was related to the intensity of smoking. For those in the lowest tertile of pack-years of smoking, the relative risk was 0.33. This study, which extended over a period of 19 years and in contrast with the studies reported by Omenn, et al. (1996), indicated that carotene intake prevented lung cancer in smokers.

The association, if any, between beta-carotene intake and the incidence of malignant neoplasms was investigated in the Physician's Health Study (Hennekens, et al., 1996). The population under study was a mix of smokers and non-smokers (50% non-smokers, 39% past smokers, and 11% current smokers). The study covered about 11,000 volunteers in each of the two groups: a beta-carotene group and a placebo group. The volunteers in the beta-carotene group took 50 mg of beta-carotene every alternate day over a period of 12 years. There was no significant difference in the incidence of lung cancer between the beta-carotene group and the placebo group.

The effect of beta-carotene on the higher incidence of lung cancer could not be confirmed in the study involving two very large cohorts comprising 46,924 men and 77,283 women and spread over a follow-up period of 10 years for men and 12 years for women (Michaud, et al., 2000). The aim of this study was to examine the relation between lung cancer risk and intake of alpha carotene, beta-carotene, lutein, lycopene and beta cryptoxanthin. The pooled analysis of the data indicated that alpha carotene and lycopene intake were significantly associated with a lower risk of lung cancer. The association between beta-carotene, lutein, and beta cryptoxanthin was not significant.

The available experimental evidence does not support a cause and effect relationship between beta-carotene and vitamin A and a higher incidence of cancer.

3. Antioxidant Interference with Chemotherapy Drugs and Irradiation (Mechanistic Aspects)

Many anti-neoplastic drugs exert their toxic action on cancer cells through the production of reactive oxygen species (ROS). Fear has been spread that if antioxidants quench ROS, they will interfere with the activity of those drugs that destroy cancer cells by the production of ROS.

Antioxidants do quench ROS, but this is only one of its activities, as detailed earlier. Further, the apprehension does not seem to be justified in view of several published reports (Seifter, et al., 1984; Lockwood, et al., 1994; Ferguson and Pearson, 1996; Blasiak and Kowalik, 2001; Murlikrishnan, et al., 2001; Yam, et al., 2001; Pathak, et

al., 2002; Walker, et al., 2002), which show that vitamin C and other antioxidants actually help destroy cancer cells when used with conventional anti-cancer therapy. This therapy induces cell damage by causing apoptosis without the help of ROS (Schmitt and Lowe, 1999).

In an animal study, ascitic liver tumor (TLT)-bearing mice were given vitamin C and vitamin K3 administered i.p. before or after a single i.p. dose of six different cytotoxic drugs, all commonly used in human cancer therapy. The combination of the drug with vitamins produced a distinct chemotherapy-potentiating effect for all the drugs examined, especially when injected before chemotherapy. The possible generation of peroxides in catalase-deficient cancer cells might also be involved here (Taper, et al., 1987).

Ascorbic acid did not affect the anti-tumor activity of Adriamycin (ADR) in mice inoculated with leukemia L1210 or Ehrlich ascites carcinoma. On the other hand, it significantly improved the life of animals treated with ADR. The significant prevention of ADR-induced cardiomyopathy in guinea pigs by ascorbic acid was proven by electron microscopy (Shimpo, et al., 1991).

In clinical studies involving 18 non-randomized patients with small cell lung carcinoma, antioxidant treatment (vitamins, trace minerals, and fatty acids) combined with a conventional therapy of cyclophosphamide, Adriamycin, and vincristine with radiation prolonged the survival time of the patients (Jaakkola, et al., 1992).

Salganik (2001) hypothesized that, on the basis of the basal levels of reactive oxygen species (ROS), the human population could be divided into two types: one with low levels of ROS and the other with high levels of ROS. As such, those with low levels of ROS would be adversely affected by antioxidants, while those with high levels stood to benefit. These observations might be used to suggest that, if the administration of antioxidants has helped certain patients, they might be the ones who have high levels of ROS.

There are several presumptions here. That the human population could be divided on the basis of its ROS levels has not been established as yet. The author himself explicitly states that this needs to be confirmed by actual studies. The entire matter of ROS being quenched by antioxidants becomes irrelevant because antioxidants inflict injuries on cancer cells by several mechanisms other than those mediated by free radicals, as is evident from the various studies mentioned in this review.

Many oncologists do not recommend antioxidant use during cancer therapy for fear that they may protect cancer cells from the toxic effects of anti-neoplastic drugs. It has been argued by some scientists that antioxidants may reduce certain types of toxicity associated with chemotherapy. It is feared that this action of antioxidants may interfere with the efficacy of chemotherapy (Labriola and Livingston, 1999; Agus, et al., 1999).

It is interesting that there is substantial evidence suggesting that antioxidants can enhance the efficiency of anti-neoplastic drugs. Conklin (2000) points out that the administration of some anti-neoplastic agents results in

oxidative stress, i.e., the production of free radicals and other reactive oxygen species (ROS). Oxidative stress reduces the cancer cell proliferation rate that occurs during chemotherapy and may interfere with the cytotoxic effects of anti-neoplastic drugs, which depend upon the rapid proliferation of cancer cells for optimal activity. Conklin reviewed several experiments and came to the conclusion that detoxification of ROS may enhance the anti-cancer effects of chemotherapy. ROS can cause or contribute to certain side effects that are common to many anti-cancer drugs, such as gastrointestinal toxicity and mutagenesis. ROS may also contribute to the side effects that occur specific to certain chemotherapeutic agents, such as doxorubicin I-induced cardiotoxicity, Cisplatin-induced nephrotoxicity, and Bleomycin-induced pulmonary fibrosis. The review indicates that, if anything, antioxidants can actually provide relief to patients from the adverse effects of the drugs and enhance the anti-cancer effects of chemotherapy.

4. Issues Related to the Use of Antioxidant Megadoses

Recently, Dr. Norman, of the American Institute of Cancer Research, and his group published a "guide intended to provide advice about dietary supplements for cancer survivors who are still being treated, their families, their physicians and the research community." (Norman, et al., 2003) Their recommendation for cancer patients was for them to take only moderate doses of supplements because the evidence from human studies that confirmed their safety and benefit was limited (NRC, 1989). The argument against using supplemental antioxidants during chemotherapy is that they may interfere with the oxidative breakdown of cellular DNA and the cell membranes necessary for the agents to work (Labriola and Livingstone, 1999; Kong and Lillehei, 1998).

Further, arguments for avoiding the addition of large doses of antioxidants during cancer therapy come from evidence that the apoptotic break down of tumor cells is selectively increased by the presence of reactive oxygen species within the tissues, and that this process will be slowed down by an antioxidant-replete diet (Salganik, et al., 2000). They, however, go on to suggest that "further research is needed to establish the clinical implications of various doses." Another comment suggested, "However, more research is needed before definitive positive or negative advice can be given about the use of antioxidant dietary supplements as adjuncts to cancer chemotherapy or radiotherapy." Evidently, these researchers were reluctant to consider information that was already available to them.

It is interesting to read what the Food and Nutrition Board (2002) had to say about RDA values: "The RDA is intended to establish guidelines for preventing nutrient deficiencies and promoting health in the majority of healthy persons." These guidelines do not necessarily apply to individuals suffering from chronic illness or individuals under metabolic stress. The RDA may be especially insufficient to maintain plasma antioxidant levels in patients undergoing high-dose chemotherapy.

We cited several studies earlier that indicate cancer patients have low levels of vitamin C (Anthony, et al., 1982; Nunez, et al., 1995; Kurbacher, et al., 1996; Gackowski, et al., 2002) and proline (Chubinskaia, et al., 1989; Okazaki, et al., 1992). We should add to these the findings of several clinical studies that clearly show the bene-

fits of using megadoses of antioxidant vitamins in the treatment of cancer. In clinical studies reported by Pathak, et al. (2002), it was observed that patients receiving 6,100 mg of ascorbic acid, 1,050 mg of d-alpha-tocopherol succinate, 60 mg of beta-carotene and a trace mineral mixture along with chemotherapy benefited, as evaluated by the number of patients in whom the cancer did not progress, number of survivals over a period of one year, and partial response of the patients.

A randomized pilot trial (Phase I/II) in Stage 0-III breast cancer patients receiving radiation therapy involved a high-dose multiple antioxidant oral preparation containing 8 g of vitamin C as calcium ascorbate, 800 IU of vitamin E as alpha-tocopheryl succinate, and 60 mg of natural beta-carotene divided in two doses (Walker, et al., 2002). Out of 25 patients receiving radiation alone, two developed new cancers, while no new cancers were detected in 22 patients receiving radiation and antioxidants.

The studies of Jaakkola, et al. (1992) and Lockwood, et al. (1994) cited earlier indicate the beneficial effects of large doses of multiple antioxidants. The studies of Lamm, et al. in particular show that higher doses of antioxidants offer many more benefits to patients than vitamins given at RDA levels.

Several research groups are now recommending the use of a combination of higher doses of antioxidants along with chemotherapy in cancer patients. A convention of medical practitioners, epidemiologists, nutritionists and others held at the Bristol Cancer Help Center formulated a consensus statement regarding nutritional guidelines for cancer patients (Goodman, et al., 1994). After examining the available evidence, they recommended the use of 6 to 10 g per day of vitamin C in active cancer patients. They did not offer any reason for stopping vitamin C supplementation during radiation and chemotherapy.

They also recommended nutrient supplements for individuals in both active and maintenance stages of cancer treatments (Table 7).

Table 7. Suggested daily supplement levels for cancer patients

Nutrient	Active Cancer	Maintenance Level
Vitamin A	10,000 IU	7,500 IU
Beta-Carotene	25,000 IU	10,000 IU
Vitamin B Complex	50 mg	50 mg
Vitamin C	6-10 g	1-3 g
Vitamin E	200-400 IU	100 IU
Zinc (Elemental)	15-25 mg	15 mg

Selenium	200 mcg	100 mcg
Chromium GTF	100 mcg	50 mcg
Magnesium	100-200 mg	100-200 mg

A new approach to cancer based on Cellular Medicine takes advantage of the effectiveness of nutrient synergy. Supported by scientific research results and numerous cases of testimonial evidence, the following Cellular Medicine recommendations can be applied in the prevention and therapeutic aspects of cancer. This nutrient combination has demonstrated an inhibitory effect on angiogenesis, cancer cell proliferation, cancer metastasis and the induction of apoptosis in cancer cells. It would thus be clear that the apprehension regarding the use of antioxidants and other essential nutrients is misplaced. This essential nutrient program should be applied in addition to a basic multivitamin/mineral/essential nutrient program taken daily as a necessary step to control cellular nutrient deficiencies and correct metabolic imbalances brought on by pathological conditions (Table 8).

Table 8. Cellular Medicine recommendations in cancer

Nutrient	Cancer Metabolic Correction (Low Ranges)	Cancer Metabolic Intervention (High Ranges)
Vitamin C	350 - 700 mg	5 > 10 g
Lysine	500 - 1,000 mg	2,000 - 5,000 mg
Proline	375 - 750 mg	1,500 - 4,000 mg
Arginine	250 - 500 mg	1,000 - 2,000 mg
N-Acetyl Cysteine	100 - 200 mg	400 - 1,000 mg
EGCG (from green tea)	500 - 1,000 mg	2,000 - 4,000 mg
Selenium	15 - 30 mcg	60 - 120 mcg
Copper	1 - 2 mg	4 mg
Manganese	0.5 - 1 mg	2 - 4 mg

It has become a matter of urgency that further well-designed trials with multiple antioxidants and other essential nutrients are conducted to document the value of natural-based programs in the prevention and treatment of cancer. In addition, further human trials need to establish nutrient efficacy when administered

before, during, and after standard therapy.

Conclusions

An evaluation of the existing clinical and research information enlisted in this review leads to the following conclusions:

- A. Antioxidants and other essential nutrients affect the neoplastic process by exerting various mechanisms in addition to their antioxidant activity. They show anti-proliferative effects, act as anti-metastatic and anti-angiogenic agents, and promote apoptosis in cancer cells. They also provide immediate relief to the patient by reducing the toxicity of chemotherapy.
- B. The clinical studies reported to date cannot provide uniform guidance in developing standard protocols in cancer therapy. They vary in study design, timings of observation/intervention, intervention protocol, malignancy and anti-cancer regimen. The studies also vary with respect to doses of various antioxidants and the combinations of antioxidants used.
- C. A novel and promising approach to cancer control is based on a scientific concept developed by Rath, et al. (1992). It utilizes the metabolic synergy of essential nutrients, such as ascorbic acid and lysine, in affecting the common mechanism of cancer growth and metastasis: the enzymatic destruction of ECM. Further research along this new therapeutic strategy has shown that the synergistic effect of these two micronutrients is enhanced by the inclusion of proline, arginine, N-acetyl cysteine and green tea extract. The already available scientific and clinical confirmation of this novel therapeutic approach suggests that a universal anti-cancer therapy has been identified. Studies conducted at the Institute have shown the multiple anti-cancer effects of the combination of these nutrients (NS) against several types of cancer cells, both in tissue cultures and laboratory animal studies. Several patients who volunteered to use this approach have benefited from it and provided testimonials to that effect.
- D. Antioxidants and other nutrients can work synergistically with conventional chemotherapy agents in cancer patients. The apprehension that higher doses of antioxidants are toxic to the body is not validated.
- E. Well-designed, large-scale clinical studies in cancer patients using the Cellular Medicine approach need to be conducted so that information about the benefits of this approach can be convincingly extended to concerned physicians and, through them, to cancer patients around the world.

The use of nutrient-based approaches is significantly more affordable and safer than conventional pharmaceuti-

More information can be found at
www.drrathresearch.org.

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cal drugs. Therefore, the use of these essential nutrients would tremendously reduce the cost of treatment of chronic conditions such as cancer. The new research direction outlined in this review, in conjunction with clinical information on nutrient-based cancer therapies, should encourage researchers and clinicians to take advantage of nutrient synergy in clinical medicine.



Dr. Matthias Rath

About Matthias Rath, M.D. and His Mission

Dr. Matthias Rath has devoted his life to conducting research in natural health approaches in the control of cancer and cardiovascular disease and applying his discoveries in these areas for the benefit of human health. Dr. Rath worked in close collaboration with the late two-time Nobel Laureate Linus Pauling, and has published several papers on the use of nutrients in various chronic conditions, particularly in the control of cancer and atherosclerosis. He has documented his natural health discoveries in a series of bestselling books, including *Cancer* and *Why Animals Don't Get Heart Attacks...But People Do!* Dr. Rath is a well-known lecturer and an internationally recognized proponent of the people's right to natural health.



Aleksandra Niedzwiecki, Ph.D.

Dr. Rath founded the Dr. Rath Research Institute of Cellular Medicine to conduct and promote research in natural health that leads to the development of nutrient-based therapies for common chronic conditions, including cancer, coronary heart disease, hypertension, arthritis, diabetes and others.

His dedicated research group is led by Aleksandra Niedzwiecki, Ph.D., FACN, a biochemist who has worked directly with two Nobel Laureates and who formerly served as the director of cardiovascular research at the Linus Pauling Institute (USA).

The Matthias Rath research team, comprising scientists holding doctoral degrees, medical degrees, and other professional credentials, has presented its work at numerous scientific and clinical conferences and published its scientific findings in peer-reviewed journals.

The research contributions of Dr. Rath have brought us closer to understanding the complex nature of chronic disease and new directions in the research a



brought
up



Matthias Rath, M.D., the successor of the late two-time Nobel Laureate Dr. Linus Pauling, has led breakthroughs in the natural control of cancer, cardiovascular disease, and other chronic health conditions.

Additional Cellular Health research is documented in the following publications:

The Cellular Health series authored by Matthias Rath, M.D.:

- *Cancer*
- *Why Animals Don't Get Heart Attacks...But People Do!*
- *Ten Years That Changed Medicine Forever*

Scientific Publications:

- *Progress in Cellular Medicine: Cellular Medicine Success in Osteosarcoma (Bone Cancer)*
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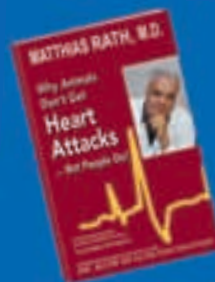
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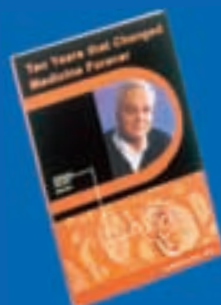
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