Vitamin C:

Craig, W. J. (1997). "Phytochemicals: guardians of our health." J Am Diet Assoc **97**(10 Suppl 2): S199-204.

Consuming a diet rich in plant foods will provide a milieu of phytochemicals, nonnutritive substances in plants that possess health-protective benefits. Nuts, whole grains, fruits, and vegetables contain an abundance of phenolic compounds, terpenoids, pigments, and other **natural antioxidants that have been associated with protection from and/or treatment of chronic disease such as heart disease, cancer, diabetes, and hypertension as well as other medical conditions**. The foods and herbs with the highest anticancer activity include garlic, soybeans, cabbage, ginger, licorice, and the umbelliferous vegetables. Citrus, **in addition to providing an ample supply of vitamin C, folic acid, potassium, and pectin, contains a host of active phytochemicals. The phytochemicals in grains reduce the risk of cardiovascular disease and cancer.**

Steinmetz, K. A. and J. D. Potter (1996). "Vegetables, fruit, and cancer prevention: a review." J Am Diet Assoc **96**(10): 1027-39.

In this review of the scientific literature on the relationship between vegetable and fruit consumption and risk of cancer, results from **206 human epidemiologic studies and 22 animal studies are summarized**. The evidence for a protective effect of greater vegetable and fruit consumption is consistent for cancers of the stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas, and colon. **The types of vegetables or fruit that most often appear to be protective against cancer are raw vegetables, followed by allium vegetables, carrots, green vegetables, cruciferous vegetables, and tomatoes.** Substances present in vegetables and fruit that may help protect against cancer, and their mechanisms, are also briefly reviewed; these include **dithiolthiones, isothiocyanates, indole-3-carbinol, allium compounds, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, vitamin C, D-limonene, lutein, folic acid, beta carotene, lycopene, selenium, vitamin E, flavonoids, and dietary fiber.** Current US vegetable and fruit intake, which averages about 3.4 servings per day, is discussed, as are possible noncancer-related effects of increased vegetable and fruit consumption, including benefits against cardiovascular disease, diabetes, stroke, obesity, diverticulosis, and cataracts. Suggestions for dietitians to use in counseling persons toward increasing vegetable and fruit intake are presented.

Jonas, C. R., A. B. Puckett, et al. (2000). "Plasma antioxidant status after high-dose chemotherapy: a randomized trial of parenteral nutrition in bone marrow transplantation patients." Am J Clin Nutr **72**(1): 181-9.

BACKGROUND: **Chemotherapy and radiation therapy result in increased free radical formation and depletion of tissue antioxidants.** It is not known whether parenteral nutrition (PN) administered during bone marrow transplantation (BMT) supports systemic antioxidant status. OBJECTIVE: **The aims of the study were to determine 1) whether high-dose chemotherapy decreases concentrations of major circulating antioxidants in patients undergoing BMT and 2) whether administration of standard PN maintains systemic antioxidant concentrations compared with PN containing micronutrients and minimal lipids alone.** DESIGN: Twenty-four BMT patients were randomly assigned to receive either standard PN containing conventional amounts of dextrose, amino acids, micronutrients, and lipid (120 kJ/d) or a solution containing only micronutrients (identical to those in standard PN) and a small amount of lipid (12 kJ/d). Plasma antioxidant status was measured before conditioning therapy and serially at days 1, 3, 7, 10, and 14 after BMT. RESULTS: **Plasma glutathione (GSH) and alpha- and gamma-tocopherol concentrations decreased and the GSH redox state became more oxidized after conditioning chemotherapy.** Plasma cysteine concentrations were unchanged, whereas cystine concentrations increased. Plasma vitamin C and zinc concentrations and GSH peroxidase activity increased over time. Plasma alpha-tocopherol concentrations were lower in patients given standard PN. There were no differences in other plasma antioxidants between groups. CONCLUSIONS: **A significant decline in GSH-glutathione disulfide, cysteine-cystine, and vitamin E status occurs after chemotherapy and BMT. Standard PN does not improve antioxidant status compared with administration of micronutrients alone.** Further evaluation of PN formulations to support patients undergoing high-dose chemotherapy and BMT are needed.

Head, K. A. (1998). "Ascorbic acid in the prevention and treatment of cancer." Altern Med Rev **3**(3): 174-86.

Proposed mechanisms of action for ascorbic acid **(ascorbate, vitamin C) in the prevention and treatment of cancer include enhancement of the immune system, stimulation of collagen formation necessary for "walling off" tumors, inhibition of hyaluronidase which keeps the ground substance around the tumor intact and prevents metastasis, prevention of oncogenic viruses, correction of an ascorbate deficiency often seen in cancer patients, expedition of wound healing after cancer surgery, enhancement of the effect of certain**

chemotherapy drugs, reduction of the toxicity of other chemotherapeutic agents such as Adriamycin, prevention of free radical damage, and neutralization of carcinogenic substances. Scottish as well as Japanese studies have pointed to the potential benefit of high dose vitamin C for the treatment of "terminal" cancer. Mayo Clinic studies, however, have contradicted the Scottish and Japanese findings, resulting in accusations of methodological flaws from both sides. **Numerous epidemiological studies have pointed to the importance of dietary and supplemental ascorbate in the prevention of various types of cancer including bladder, breast, cervical, colorectal, esophageal, lung, pancreatic, prostate, salivary gland, stomach, leukemia, and non-Hodgkin's lymphoma.**

Creagan, E. T., C. G. Moertel, et al. (1979). "Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial." N Engl J Med **301**(13): 687-90.

One hundred and fifty patients with advanced cancer participated in a controlled double-blind study to evaluate the effects of high-dose vitamin C on symptoms and survival. Patients were divided randomly into a group that received vitamin C (10 g per day) and one that received a comparably flavored lactose placebo. Sixty evaluable patients received vitamin C and 63 received a placebo. Both groups were similar in age, sex, site of primary tumor, performance score, tumor grade and previous chemotherapy. The two groups showed no appreciable difference in changes in symptoms, performance status, appetite or weight. The median survival for all patients was about seven weeks, and the survival curves essentially overlapped. **In this selected group of patients, we were unable to show a therapeutic benefit of high-dose vitamin C treatment**.

Liu, Q. Y. and B. K. Tan (2000). "Effects of cis-unsaturated fatty acids on doxorubicin sensitivity in P388/DOX resistant and P388 parental cell lines." Life Sci **67**(10): 1207-18.

It has been reported that several cis-unsaturated fatty acids (c-UFAs) could increase doxorubicin (DOX) accumulation in cancer cells and hence elevate its cytotoxicity. However, some researchers showed that c-UFA pretreatment did not affect its cytotoxicity in special cell lines. It is possible that the different results occurred due to different cellular characteristics. We hypothesized that c-UFA treatment might modulate the activities of some antioxidant enzymes to affect the resistance of cells to DOX. In the present study, we examined how c-UFA pretreatment affected DOX cytotoxicity on mouse leukemia cell line, P388, and its resistant subline, P388/DOX, which we found to have significantly higher glutathione peroxidase (GPx) activity as well as P-glycoprotein (p-gp)

overexpression. We chose two c-UFAs, gamma-linolenic acid (GLA) (18:3n-6) and docosahexaenoic acid (DHA) (22:6n-3). Cytotoxicity was measured by MTT (3-(4.5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and trypan blue exclusion assays. DOX accumulation and p-gp expression were measured by flow cytometry. The activities of catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), and GPx were determined for both cell lines with and without treatment with GLA or DHA. **Significant DOX accumulation occurred in both cell lines with GLA or DHA pretreatment, but without any change in p-gp expression in either cell line.** Sensitivity to DOX cytotoxicity was improved by GLA or DHA pretreatment in P388/DOX in which only SOD activity was significantly increased, but not in the parental cell line P388 in which both SOD and CAT were significantly increased by the pretreatment. **However, combined pretreatment of GLA or DHA with antioxidants, pyrrolidinedithiocarbamate (PDTC) or Vitamin C, could sensitize not only P388/DOX but also P388 cells to DOX**. We conclude that the effects of c-UFA pretreatment on the sensitivity of cancer cells to DOX not only depend on the change in drug accumulation but also the change in the levels of antioxidant enzyme activities, and **suggest that combined administration of c-UFAs, antioxidants, and DOX may be more effective in treating leukemia.**

Weijl, N. I., T. J. Elsendoorn, et al. (2004). "Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study." Eur J Cancer **40**(11): 1713-23.

Cisplatin-induced toxicities are mainly caused by the formation of free radicals, leading to oxidative organ damage. Plasma concentrations of antioxidants decrease significantly during cisplatin chemotherapy for cancer. Forty-eight cancer patients treated with cisplatin-based chemotherapy were randomised in a double-blind manner to receive either supplementation with vitamin C, vitamin E and selenium dissolved in a beverage or to receive a placebo beverage. Primary outcome measures were the amount of nephrotoxicity and ototoxicity induced by cisplatin. No significant differences were found between the two study groups with respect to these primary outcome measures. However, **patients who achieved the highest plasma concentrations of the three antioxidant micronutrients had significantly less loss of high-tone hearing**. In addition, significant correlations were found between the reduced/oxidised vitamin C ratio and malondialdehyde (MDA), markers of oxidative stress, and cisplatin-induced ototoxicity and nephrotoxicity. The lack of protection against cisplatin-induced toxicities in patients in the intervention arm may be related to poor compliance and/or inadequate supplementation.

Supplementation with a higher dose (intensity) and in combination with other antioxidants should be investigated further.

Padayatty, S. J., H. Sun, et al. (2004). "Vitamin C pharmacokinetics: implications for oral and intravenous use." Ann Intern Med **140**(7): 533-7.

BACKGROUND: **Vitamin C at high concentrations is toxic to cancer cells in vitro.** Early clinical studies of vitamin C in patients with terminal cancer suggested clinical benefit, but 2 double-blind, placebo-controlled trials showed none. However, these studies used different routes of administration. OBJECTIVE: **To determine whether plasma vitamin C concentrations vary substantially with the route of administration**. DESIGN: Dose concentration studies and pharmacokinetic modeling. SETTING: Academic medical center. PARTICIPANTS: 17 healthy hospitalized volunteers. MEASUREMENTS: Vitamin C plasma and urine concentrations were measured after administration of oral and intravenous doses at a dose range of 0.015 to 1.25 g, and plasma concentrations were calculated for a dose range of 1 to 100 g. RESULTS: Peak plasma vitamin C concentrations were higher after administration of intravenous doses than after administration of oral doses ($P < 0.001$), and the difference increased according to dose. Vitamin C at a dose of 1.25 g administered orally produced mean (+/-sd) peak plasma concentrations of 134.8 +/- 20.6 micromol/L compared with 885 +/- 201.2 micromol/L for intravenous administration. For the maximum tolerated oral dose of 3 g every 4 hours, pharmacokinetic modeling predicted peak plasma vitamin C concentrations of 220 micromol/L and 13 400 micromol/L for a 50-g intravenous dose. Peak predicted urine concentrations of vitamin C from intravenous administration were 140-fold higher than those from maximum oral doses. LIMITATIONS: Patient data are not available to confirm pharmacokinetic modeling at high doses and in patients with cancer. CONCLUSIONS: Oral vitamin C produces plasma concentrations that are tightly controlled. **Only intravenous administration of vitamin C produces high plasma and urine concentrations that might have antitumor activity.** Because efficacy of vitamin C treatment cannot be judged from clinical trials that use only oral dosing, the role of vitamin C in cancer treatment should be reevaluated.

Gonzalez, M. J., J. R. Miranda-Massari, et al. (2002). "Orthomolecular oncology: a mechanistic view of intravenous ascorbate's chemotherapeutic activity." P R Health Sci J **21**(1): 39-41.

The effect of vitamin C in cancer has been a subject of great controversy; mainly because of the inconsistent results obtained by oral intakes of ascorbate when used as an anticancer agent. **We believe the intravenous application of ascorbate will provide more consistent results in cancer patients since Vitamin C blood levels attained are**

substantially higher in a range proven cytotoxic to malignant cells. In this article we will present and discuss our proposed mechanism on the chemotherapeutic activity exhibited by ascorbate.

Drisko, J. A., J. Chapman, et al. (2003). "The use of antioxidant therapies during chemotherapy." Gynecol Oncol **88**(3): 434-9.

OBJECTIVE: At the present time, **many cancer patients combine some form of complementary and alternative medicine therapies with their conventional therapies. The most common choice of these therapies is the use of antioxidants.** RESULTS: A review of four common antioxidants is undertaken, which includes vitamin E (mixed tocopherols and tocotrienols), beta-carotene (natural mixed carotenoids), vitamin C (ascorbic acid), and vitamin A (retinoic acid). **Antioxidants act as electron acceptors as well as therapeutic biologic response modifiers**. Despite the fact that chemotherapy-induced formation of free radicals is well-demonstrated, **chemotherapy-induced cytotoxicity in general does not seem to depend on formation of reactive oxygen species.** CONCLUSIONS: **Currently, evidence is growing that antioxidants may provide some benefit when combined with certain types of chemotherapy.** Because of the potential for positive benefits, a randomized controlled trial evaluating the safety and efficacy of adding antioxidants to chemotherapy in newly diagnosed ovarian cancer is underway at the University of Kansas Medical Center.

Cameron, E. (1991). "Protocol for the use of vitamin C in the treatment of cancer." Med Hypotheses **36**(3): 190-4.

A protocol for the **use of vitamin C in the treatment of cancer**, developed over a number of years in Vale of Leven Hospital, Scotland, is presented. **Clinical experience has shown this protocol to be both safe and efficient**. It need not be followed 'to the letter', but provides general guidance to physicians unfamiliar with this therapeutic approach. **It recommends that all cancer patients treated in this fashion be given an initial course of intravenous ascorbate followed by a maintenance oral dose to be continued indefinitely thereafter. The importance of continuous as opposed to intermittent administration is emphasized.**

Standish, L. J., K. Greene, et al. (2002). "Complementary and alternative medical treatment of breast cancer: a survey of licensed North American naturopathic physicians." Altern Ther Health Med **8**(5): 68-70; 72-5.

CONTEXT: Complementary and alternative medicine (CAM) use is on the rise in the United States, especially for breast cancer patients. **Many CAM therapies are delivered by licensed naturopathic physicians using individualized treatment plans.** OBJECTIVE: **To describe**

naturopathic treatment for women with breast cancer. DESIGN: Cross-sectional mail survey in 2 parts: screening form and 13-page survey. SETTING: Bastyr University Cancer Research Center, Kenmore, Wash. PARTICIPANTS: All licensed naturopathic physicians in the United States and Canada (N=1,356) received screening forms; 642 (47%) completed the form. Of the respondents, 333 (52%) were eligible, and 161 completed the survey (48%). MAIN OUTCOME MEASURES: Demographics of naturopathic physicians, development of treatment plans, CAM therapies used, perceived efficacy of therapeutic interventions. RESULTS: Of those respondents screened, 497 (77%) had provided naturopathic care to women with breast cancer, and 402 (63%) had treated women with breast cancer in the previous 12 months. Naturopaths who were women were more likely than men to treat breast cancer (P < or = .004). Of the survey respondents, 104 (65%) practiced in the United States, and 57 (35%) practiced in Canada; 107 (66.5%) were women, and 54 (33.5%) were men. **To develop naturopathic treatment plans, naturopathic physicians most often considered the stage of cancer, the patient's emotional constitution, and the conventional therapies used.** To monitor patients clinically, 64% of the naturopathic physicians used diagnostic imaging, 57% considered the patient's quality of life, and 51% used physical examinations. The most common general CAM therapies used were dietary counseling (94%), botanical medicines (88%), antioxidants (84%), and supplemental nutrition (84%). **The most common specific treatments were vitamin C (39%), coenzyme Q-10 (34%), and Hoxsey formula (29%).**

Prasad, K. N., A. Kumar, et al. (1999). "High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy." J Am Coll Nutr **18**(1): 13-25.

Numerous articles and several reviews have been published on the role of antioxidants, and diet and lifestyle modifications in cancer prevention. However, the potential role of these factors in the management of human cancer have been largely ignored. Extensive in vitro studies and limited in vivo studies have revealed that individual antioxidants such as vitamin A (retinoids), vitamin E (primarily alpha-tocopheryl succinate), vitamin C (primarily sodium ascorbate) and carotenoids (primarily polar carotenoids) induce cell differentiation and growth inhibition to various degrees in rodent and human cancer cells by complex mechanisms. The proposed mechanisms for these effects include inhibition of protein kinase C activity, prostaglandin E1-stimulated adenylate cyclase activity, expression of c-myc, H-ras, and a transcription factor (E2F), and induction of transforming growth factor-beta and p21 genes. Furthermore, antioxidant vitamins individually or in combination enhance the growth-inhibitory effects of x-irradiation, chemotherapeutic agents, hyperthermia, and biological

response modifiers on tumor cells, primarily in vitro. **These vitamins, individually, also reduce the toxicity of several standard tumor therapeutic agents on normal cells. Low fat and high fiber diets can further enhance the efficacy of standard cancer therapeutic agents; the proposed mechanisms for these effects include the production of increased levels of butyric acid and binding of potential mutagens in the gastrointestinal tract by high fiber and reduced levels of growth promoting agents such as prostaglandins, certain fatty acids and estrogen by low fat.** We propose, therefore, a working hypothesis that multiple antioxidant vitamin supplements together with diet and lifestyle modifications may improve the efficacy of standard and experimental cancer therapies.

Prasad, K. N., W. C. Cole, et al. (2002). "Pros and cons of antioxidant use during radiation therapy." Cancer Treat Rev **28**(2): 79-91.

Radiation therapy is one of the major treatment modalities in the management of human cancer. While impressive progress like more accurate dosimetry and more precise methods of radiation targeting to tumor tissue has been made, the value of radiation therapy in tumor control may have reached a plateau. **At present, two opposing hypotheses regarding the use of antioxidants during radiation therapy have been proposed. One hypothesis states that supplementation with high doses of multiple micronutrients including high dose dietary antioxidants (vitamins C and E, and carotenoids) may improve the efficacy of radiation therapy by increasing tumor response and decreasing some of its toxicity on normal cells. The other hypothesis suggests that antioxidants (dietary or endogenously made) should not be used during radiation therapy, because they would protect cancer cells against radiation damage**. Each of these hypotheses is based on different conceptual frameworks that are derived from results obtained from specific experimental designs, and thus, **each may be correct within its parameters.** The question arises whether any of these concepts and experimental designs can be used during radiation therapy to improve the management of human cancer by this modality. **This review has analyzed published data that are used in support of each hypothesis, and has revealed that the current controversies can be resolved, if the results obtained from one experimental design are not extrapolated to the other. This review has also discussed the scientific rationale for a micronutrient protocol that includes high doses of dietary antioxidants (vitamin C, vitamin E succinate and natural beta-carotene) which can be used adjunctively with radiation therapy.**

Calderon, P. B., J. Cadrobbi, et al. (2002). "Potential therapeutic application of the association of vitamins C and K3 in cancer treatment." Curr Med Chem **9**(24): 2271-85.

> **The decision of stressed cells to die or to survive is made by integrating signals at different levels through multiple check points. However, initiation and continued progression toward cell death by apoptosis in cancer cells may be blocked by mutation of the tumor suppressor p53 or overexpression of members of the bcl-2 family of proteins. The existence of such mechanisms indicates that cancer cells lose the controls regulating their cell cycle.** Therefore, the activation of their programmed cell death appears as a major therapeutic target. Oxidative stress can stimulate growth, trigger apoptosis, or cause necrosis depending upon the dose and the exposure time of the oxidizing agent. **A large body of evidence supports the idea that oxidative stress induced by redox cycling of vitamins C and K(3) in association surpasses cancer cellular defense systems and results in cell death.** The molecular mechanisms underlying such a process are, however, still unknown. Indeed, several types of cell death may be produced, namely autoschizis, apoptosis and necrosis. **Combined vitamin C and K(3) administration in vitro and in vivo produced tumor growth inhibition and increased the life-span of tumor-bearing mice. CK(3)-treatment selectively potentiated tumor chemotherapy, produced sensitization of tumors resistant to some drugs, potentiated cancer radiotherapy and caused inhibition of the development of cancer metastases without inducing toxicity in the host. We propose the association of vitamins C and K(3) as an adjuvant cancer therapy which may be introduced into human cancer therapy without any change in the classical anticancer protocols, and without any supplementary risk for patients.**

De Loecker, W., J. Janssens, et al. (1993). "Effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K3) treatment on human tumor cell growth in vitro. II. Synergism with combined chemotherapy action." Anticancer Res **13**(1): 103-6.

> **The growth inhibitory effects of a combined application of sodium ascorbate (Vitamin C) and 2-methyl-1,4-naphthoquinone (Vitamin K3) together with various chemotherapeutic agents has been examined on in vitro cultured human endometrial adenocarcinoma (AN3CA) cells.** Combined vitamin treatment and chemotherapy in well defined conditions of cell confluence and at the dose levels applied result in a synergistic effect on growth inhibition. **The combined vitamins when reaching their own synergistic cytotoxicity levels frequently obscure the additional synergistic effects attributable to the chemotherapeutic agents.** Apart from the specific cytotoxic

characteristics of the chemotherapeutic drugs examined, the formation of reactive oxygen radicals during treatment, possibly accentuated by less defined secondary mechanisms, appears essentially responsible for the observed stimulated cytotoxicity.

Taper, H. S. and M. Roberfroid (1992). "Non-toxic sensitization of cancer chemotherapy by combined vitamin C and K3 pretreatment in a mouse tumor resistant to oncovin." Anticancer Res **12**(5): 1651-4.

The effects of combined vitamin C and K3 i.p. injected 3 hours before i.p. administration of single dose of oncovin, to which the ascites liver tumor in mouse (T.L.T.) was completely resistant, were investigated. **This pretreatment sensitized the tumor resistant to oncovin,** whereas a separate pretreatment with vitamin C or K3 alone was without any effect. This tumor sensitization to the chemotherapy was completely suppressed by catalase pretreatment, thus indicating that hydrogen peroxide generation with subsequent oxidative stress and its consequences may be involved here. Since this sensitization was without any increased general and organ toxicity, its possible introduction into classical protocols of human cancer treatment would be without any supplementary risk.

Taper, H. S., J. de Gerlache, et al. (1987). "Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment." Int J Cancer **40**(4): 575-9.

The influence on the survival of ascitic liver tumor (TLT)-bearing mice of combined vitamins C and K3 administered before or after a single i.p. dose of 6 different cytotoxic drugs, all commonly used in human cancer therapy, was investigated. **Combined i.p. administration of these vitamins produced a distinct chemotherapy-potentiating effect for all drugs examined, especially when injected before chemotherapy**. This potentiating treatment did not increase the general and organ toxicity that accompanies cancer chemotherapy. The possible generation of peroxides followed by membrane lipid alteration, DNase activation and DNA destruction by combined vitamin C and K3 in catalase-deficient cancer cells might be involved in the mechanisms of this selective potentiation.

Maramag, C., M. Menon, et al. (1997). "Effect of vitamin C on prostate cancer cells in vitro: effect on cell number, viability, and DNA synthesis." Prostate **32**(3): 188-95.

BACKGROUND: Many studies describe the protective role of vitamin C (ascorbic acid) against cancer development and in treatment of established cancer. The present study investigated whether ascorbic acid demonstrates a therapeutic benefit for prostate cancer. METHODS: Androgen-independent (DU145) and androgen-dependent (LNCaP)

human prostate cancer cell lines were both treated in vitro with vitamin C (0-10 mM). Cell counts, cell viability, and thymidine incorporation into DNA were determined. RESULTS: **Treatment of DU145 and LNCaP cells with vitamin C resulted in a dose- and time-dependent decrease in cell viability and thymidine incorporation into DNA. Vitamin C induced these changes through the production of hydrogen peroxide**; addition of catalase (100-300 units/ml), an enzyme that degrades hydrogen peroxide, inhibited the effects of ascorbic acid. Superoxide dismutase, an enzyme that dismutates superoxide and generates hydrogen peroxide, did not prevent decreases in cell number and DNA synthesis, suggesting further the involvement of hydrogen peroxide in vitamin C-induced changes. **These results clearly indicate that reactive oxygen species (ROS) are involved in vitamin C-induced cell damage.** However, that 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 suggests that vitamin C-induced changes do not occur through the generation of these ROS. CONCLUSIONS: **Vitamin C inhibits cell division and growth through production of hydrogen peroxide, which damages the cells probably through an as yet unidentified free radical(s) generation/mechanism**. Our results also suggest that ascorbic acid is a potent anticancer agent for prostate cancer cells.

Venugopal, M., J. M. Jamison, et al. (1996). "Synergistic antitumor activity of vitamins C and K3 on human urologic tumor cell lines." Life Sci **59**(17): 1389-400.

A micro-tetrazolium assay was employed to **evaluate vitamin C (VC), vitamin K3 (VK3) and vitamin C/vitamin K3 combinations (VC/VK3) for their antitumor activity against eight human urologic tumor cell lines.** While the individual vitamins exhibited antitumor activity at high concentrations, co-administration of the vitamins in a VC : VK3 ratio of 100 : 1 potentiated antitumor activity 4- to 61-fold even when exposure times were as short as 1 hour. Administration of exogenous catalase destroyed the antitumor activity of the vitamins and suggested that hydrogen peroxide and perhaps other reactive oxygen species were involved in the antitumor mechanism of these vitamins. Electron micrographs taken in a previous study demonstrated that vitamin treatment damaged mitochondria and may have impaired ATP synthesis. Analysis of cellular ATP and thiol levels as well as DNA and protein synthesis during the first five hours following a one hour VC/VK3 treatment, revealed: a transient increase in ATP production, a substantial decrease in DNA synthesis, an increase in protein synthesis and a decrease in thiol levels. **These results suggested that redox cycling of the vitamin combination increased oxidative stress until it surpassed the reducing ability of the cellular**

thiols and cellular or genetic damage ensued.

Whelan, R. L., K. D. Horvath, et al. (1999). "Vitamin and calcium supplement use is associated with decreased adenoma recurrence in patients with a previous history of neoplasia." Dis Colon Rectum **42**(2): 212-7.

INTRODUCTION**: Although some have suggested that certain vitamins or calcium supplements may reduce adenoma recurrence, our own prior retrospective study found no such effects. The purpose of this case-control study was to further investigate whether regular vitamin or calcium supplement intake influenced the incidence of recurrent adenomatous polyps in patients with previous neoplasia who were undergoing follow-up colonoscopy.** METHODS: This study enrolled 1,162 patients who underwent colonoscopy by one of three surgeons at Columbia-Presbyterian Medical Center in New York City between March 1993 and February 1997. Of these patients 448 (250 males) had a previous diagnosis of colorectal neoplasia (cancer, adenomas, or dysplasia). Of these, 183 (40.8 percent) had an adenoma at the index colonoscopy. Information was collected on personal and family history of colonic diseases, cigarette smoking, medication, and vitamin and micronutrient supplement usage on a questionnaire that was completed by the patients before the colonoscopy. Odds ratios were obtained by unconditional logistic regression analysis, adjusting for age and gender, and used adenoma recurrence at index colonoscopy as the outcome. RESULTS: The mean interval between colonoscopic examinations was 37 months for the recurrent adenoma group and 38 months for the nonrecurrent group of patients (P = not significant). In this case-control study we found a protective effect for the use of vitamin supplements in general (any vitamin) on the recurrence of adenomas (odds ratio, 0.41; 95 percent confidence interval, 0.27-0.61). Specifically, this protective effect was observed for the use of multivitamins (odds ratio, 0.47; 95 percent confidence interval, 0.31-0.72), vitamin E (odds ratio, 0.62; 95 percent confidence interval, 0.39-0.98), and for calcium supplementation (odds ratio, 0.51; 95 percent confidence interval, 0.27-0.96). Nonsignificant protective effects were noted for carotene/vitamin A, vitamin D, and vitamin C. CONCLUSIONS: **The use of multivitamins, vitamin E, and calcium supplements were found to be associated with a lower incidence of recurrent adenomas in a population of patients with history of previous colonic neoplasia.** Prospective, randomized trials are needed to better assess the impact of these agents and to determine whether the use of these supplements is associated with a protective effect against recurrent adenomas.

Lamm, D. L., D. R. Riggs, et al. (1994). "Megadose vitamins in bladder cancer: a double-blind clinical trial." J Urol **151**(1): 21-6.

Epidemiological and laboratory studies suggest that vitamin supplements may be helpful in the prevention of some cancers but clinical trials to date have failed to demonstrate protection with naturally occurring vitamins. **Without substantiation of the highly touted benefits of vitamins, few physicians who care for cancer patients have recommended their use.** A total of 65 patients with biopsy confirmed transitional cell carcinoma of the bladder enrolled in a randomized comparison of intravesical bacillus Calmette-Guerin (BCG) with or without percutaneous administration was also randomized by closed envelope to therapy with multiple vitamins in the recommended daily allowance (RDA) versus RDA multivitamins plus 40,000 units vitamin A, 100 mg. vitamin B6, 2,000 mg. vitamin C, 400 units vitamin E and 90 mg. zinc. The addition of percutaneous BCG did not significantly lessen tumor recurrence but recurrence after 10 months was markedly reduced in patients receiving megadose vitamins. The 5-year estimates of tumor recurrence are 91% in the RDA arm and 41% in the megadose arm ($p = 0.0014$, Mantel-Cox). Overall recurrence was 24 of 30 patients (80%) in the RDA arm and 14 of 35 (40%) in the high dose arm ($p = 0.0011$, 2-tailed Fisher's exact test). **Megadose vitamins A, B6, C and E plus zinc decrease bladder tumor recurrence in patients receiving BCG immunotherapy.** Further research will be required to identify which ingredient(s) provide this protection.