Vitamin E:

Jolliet, P., N. Simon, et al. (1998). "Plasma coenzyme Q10 concentrations in breast cancer: prognosis and therapeutic consequences." Int J Clin Pharmacol Ther **36**(9): 506-9.

BACKGROUND: Coenzyme Q10 or ubiquinone is a redox component of the respiratory chain, which may be involved in the pathogenesis of cancer. METHODS: In order to better understand the role of this vitamin in the pathogenesis of breast cancer, a clinical trial including 200 women hospitalized for the biopsy and/or the ablation of a breast tumor was conducted. Ubiquinone plasma concentrations were determined simultaneously with vitamin E plasma concentrations (as antioxidant reference) by HPLC. RESULTS: A coenzyme Q10 deficiency was noted both in carcinomas (80 patients) and non-malignant lesions (120 patients), while vitamin E concentrations were within the normal range. A correlation was shown between the intensity of the deficiency and the bad prognosis of the breast disease based on high TNM and SBR values or the lack of estrogen receptors. However, neither cathepsin D level nor adenopathy invasion was related to ubiquinone levels. CONCLUSIONS: Since prooxidants may promote tumorigenesis, ubiquinone supplementation in breast cancer could be relevant.

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.

High, K. P., C. Legault, et al. (2002). "Low plasma concentrations of retinol and alpha-tocopherol in hematopoietic stem cell transplant recipients: the effect of mucositis and the risk of infection." Am J Clin Nutr **76**(6): 1358-66.

BACKGROUND: Although vitamin deficiencies are rare in the United States, acute reductions in concentrations of plasma retinol (vitamin A) or alpha-tocopherol (vitamin E) have been associated with impaired immune responses in some clinical settings. OBJECTIVE: The objectives were to determine the plasma concentrations of retinol and alpha-tocopherol in patients undergoing dose-intensive therapy and hematopoietic stem cell transplant and to examine the association of plasma concentrations with clinical outcomes reflecting immunity. DESIGN: This was an observational trial of 120 consecutive recipients of hematopoietic stem cell transplant and a multivariate analysis of plasma vitamin concentrations, mucositis, infections in the first 30 d, and herpes zoster infections in the first year after hematopoietic stem cell transplant. RESULTS: Plasma retinol and alpha-tocopherol concentrations declined from baseline to day 7, typically recovering without specific replacement toward baseline by day 14. The severity of mucositis was a strong predictor of low plasma retinol on day 7 (P = 0.001). Eighty-two patients (68%) had at least one plasma retinol concentration < or = 1.05 micro mol/L, a concentration previously determined to be of immunologic significance, during the peritransplant period (day -8 to day 14). Men more frequently acquired herpes zoster than women, and men who developed hyporetinolemia (< or = 1.05 micro mol/L) had a significantly higher risk of herpes zoster (OR: 6.6; 95% CI: 1.5, 29.6). Plasma alpha-tocopherol was not associated with any clinical event measured in this study. CONCLUSION: Hyporetinolemia is common, particularly in subjects with severe mucositis, and is associated with an increased risk of herpes zoster infection in recipients of hematopoietic stem cell transplant. Additional investigations are required to determine whether these findings indicate a causal relation.

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.

Gogos, C. A., P. Ginopoulos, et al. (1998). "Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial." Cancer **82**(2): 395-402.

BACKGROUND. The aim of the current prospective, randomized control study was to investigate the effect of dietary omega-3 polyunsaturated fatty acids plus vitamin E on the immune status and survival of well-nourished and malnourished patients with generalized malignancy. METHODS. Sixty patients with generalized solid tumors were randomized to receive dietary supplementation with either fish oil (18 g of omega-3 polyunsaturated fatty acids, PUFA) or placebo daily until death. Each group included 15 well-nourished and 15 malnourished patients. The authors measured total T cells, T-helper cells, T-suppressor cells, natural killer cells, and the synthesis of interleukin-1, interleukin-6, and tumor necrosis factor by peripheral blood mononuclear cells before and on Day 40 of fish oil supplementation. Karnofsky performance status, nutritional state, and survival were also estimated. RESULTS. The ratio of T-helper cells to T-suppressor cells was significantly lower in malnourished patients. Omega-3 PUFA had a considerable immunomodulating effect by increasing this ratio in the subgroup of malnourished patients. There were no significant differences in cytokine production among the various groups, except for a decrease in tumor necrosis factor production in malnourished cancer patients, which was restored by omega-3 fatty acids.

The mean survival was significantly higher for the subgroup of well-nourished patients in both groups, whereas omega-3 fatty acids prolonged the survival of all the patients. CONCLUSIONS. Malnutrition appears to be an important predictor of survival for patients with end stage malignant disease. Omega-3 polyunsaturated fatty acids had a significant immunomodulating effect and seemed to prolong the survival of malnourished patients with generalized malignancy.

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.

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.

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.

Borek, C. (2004). "Dietary antioxidants and human cancer." Integr Cancer Ther **3**(4): 333-41.

Epidemiological studies show that a high intake of anti-oxidant-rich foods is inversely related to cancer risk. While animal and cell cultures confirm the anticancer effects of antioxidants, intervention trials to determine their ability to reduce cancer risk have been inconclusive, although selenium

and vitamin E reduced the risk of some forms of cancer, including prostate and colon cancer, and carotenoids have been shown to help reduce breast cancer risk. Cancer treatment by radiation and anticancer drugs reduces inherent antioxidants and induces oxidative stress, which increases with disease progression. Vitamins E and C have been shown to ameliorate adverse side effects associated with free radical damage to normal cells in cancer therapy, such as mucositis and fibrosis, and to reduce the recurrence of breast cancer. While clinical studies on the effect of anti-oxidants in modulating cancer treatment are limited in number and size, experimental studies show that antioxidant vitamins and some phytochemicals selectively induce apoptosis in cancer cells but not in normal cells and prevent angiogenesis and metastatic spread, suggesting a potential role for antioxidants as adjuvants in cancer therapy.

Prasad, K. N., B. Kumar, et al. (2003). "Alpha-tocopheryl succinate, the most effective form of vitamin E for adjuvant cancer treatment: a review." J Am Coll Nutr **22**(2): 108-17.

In 1982, it was established that alpha-tocopheryl succinate (alpha-TS) was the most effective form of vitamin E in comparison to alpha-tocopherol, alpha-tocopheryl acetate and alpha-tocopheryl nicotinate in inducing differentiation, inhibition of proliferation and apoptosis in cancer cells, depending upon its concentration. During the last two decades, several studies have confirmed this observation in rodent and human cancer cells in culture and in vivo (animal model). The most exciting aspect of this alpha-TS effect is that it does not affect the proliferation of most normal cells. In spite of several studies published on the anti-cancer properties of alpha-TS, the value of this form of vitamin E has not drawn significant attention from researchers and clinicians. Therefore, a critical review on the potential role of alpha-TS in the management of cancer is needed. In addition, such a review can also provide in-depth analysis of existing literature on this subject. alpha-TS treatment causes extensive alterations in gene expression; however, only some can be attributed to differentiation, inhibition of proliferation and apoptosis. alpha-TS also enhances the growth-inhibitory effect of ionizing radiation, hyperthermia, some chemotherapeutic agents and biological response modifiers on tumor cells, while protecting normal cells against some of their adverse effects. Thus, alpha-TS alone or in combination with dietary micronutrients can be useful as an adjunct to standard cancer therapy by increasing tumor response and possibly decreasing some of the toxicities to normal cells.

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.

Yam, D., A. Peled, et al. (2001). "Suppression of tumor growth and metastasis by dietary fish oil combined with vitamins E and C and cisplatin." Cancer Chemother Pharmacol **47**(1): 34-40.

PURPOSE: The anticancer activity of omega-3 polyunsaturated fatty acids (omega-3 PUFA) has been shown in a large number of studies. This study was undertaken to analyze the combined effect of omega-3 PUFA and antioxidative vitamins on the level of spontaneous metastatic dissemination. The supportive effect of this dietary combination on chemotherapy with cisplatin (CP) was determined in parallel. METHODS: C57BL/6J mice bearing the Lewis lung carcinoma 3LL were fed ad libitum one of three isocaloric diets containing 5% soybean oil supplemented with 40 mg/kg alpha-tocopherol acetate (SO diet), or 4% fish oil plus 1% corn oil, and basal amounts of vitamin E (FO diet) or FO diet supplemented with vitamins E and C (FO+E+C diet). These diets were tested in combination with the conventional cytotoxic agent CP in a series of regimens. Tumor growth, feed consumption, body weight, lung metastasis and lung histology were followed. RESULTS: Both the FO dietary groups showed significantly lower tumor development than the SO group in all

examined parameters, indicating that omega-3 PUFA have anticancer activity. However, the FO diet, in comparison with the FO+E+C diet induced a significantly slower rate of tumor growth, and lower metastatic load, as reflected in lung weight. The decrease in the anticancer activity of FO by the addition of vitamins E and C suggests that in situ oxidation of omega-3 PUFA underlies their anticancer action. It is thus proposed that oxidized omega-3 PUFA accumulates in the membranes and the cytosol of tumor cells, reducing their vitality and eventually leading to their death. No signs of anorexia or cachexia were observed in either FO group, in contrast to the SO group. CP treatment with the SO diet had no apparent therapeutic effect, while with the FO diets it reduced the metastatic load. The best regimen of this combined treatment was FO diet followed by CP treatment with FO diet supplemented with vitamins E and C after resection of the primary growth. This regimen could be translated to a combined therapy for human cancer. CONCLUSIONS: Diets enriched with omega-3 PUFA may have beneficial anticancer effects in particular when containing only basal amounts of antioxidants such as vitamin E or C. Furthermore, the addition of drugs which promote oxidation of omega-3 PUFA, such as ferrous salts (e.g. as prescribed for the treatment of anemia), may further increase these effects. However, the supportive effect of omega-3 PUFA in chemotherapy (e.g. with CP) increases when vitamins E and C are also included.

Nargi, J. L., R. R. Ratan, et al. (1999). "p53-independent inhibition of proliferation and p21(WAF1/Cip1)-modulated induction of cell death by the antioxidants N-acetylcysteine and vitamin E." Neoplasia **1**(6): 544-56.

Epidemiological evidence has suggested an association between diets rich in antioxidants and diminished risks of various types of cancer. Proposed mechanisms for protective effects of antioxidants have involved inhibition of free radical-mediated DNA damage. Recent data suggest that antioxidants may prevent or eliminate cancerous cells through their ability to inhibit proliferation or to induce programmed cell death (PCD). To begin to identify cell cycle and cell death regulatory factors involved in antioxidant-induced growth arrest and PCD, we have studied colorectal carcinoma cells (CRCs) that differ in expression of the tumor suppressor protein p53, and of the cyclin-dependent kinase (CDK) inhibitor p21(Waf1/Cip1). The antioxidants, N-acetylcysteine (NAC) and vitamin E either inhibited proliferation in a p53-independent manner without affecting cell viability or induced cell death. Growth arrest was not associated with upregulation of the CDK inhibitors p21(Waf1/Cip1), p18(ink4c) or p16(ink4a), but was associated with a decrease in reactive oxygen species (ROS). In contrast to previous observations, the absence of p21(Waf1/Cip1) increased susceptibility of CRCs to antioxidant-induced PCD. NAC decreased levels of retinoblastoma protein (Rb)

phosphorylation in all cells tested, but Rb was cleaved only in cells which underwent NAC-induced death. Although NAC decreased ROS in all cells studied, cell lines in which PCD occurred had higher baseline levels of ROS than cell lines in which proliferation was blocked. These observations suggest that expression of p21(Waf1/Cip1) and basal levels of ROS are important determinants of outcome after antioxidant treatment.

Chinery, R., J. A. Brockman, et al. (1997). "Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer: a p53-independent induction of p21WAF1/CIP1 via C/EBPbeta." Nat Med **3**(11): 1233-41.

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States. Five-fluorouracil (5FU) remains the single most effective treatment for advanced disease, despite a response rate of only 20%. Herein, we show that the antioxidants pyrrolidinedithiocarbamate and vitamin E induce apoptosis in CRC cells. This effect is mediated by induction of p21WAF1/CIP1, a powerful inhibitor of the cell cycle, through a mechanism involving C/EBPbeta (a member of the CCAAT/enhancer binding protein family of transcription factors), independent of p53. Antioxidants significantly enhance CRC tumor growth inhibition by cytotoxic chemotherapy in vitro (5FU and doxorubicin) and in vivo (5FU). Thus, chemotherapeutic agents administered in the presence of antioxidants may provide a novel therapy for colorectal cancer.

Naziroglu, M., A. Karaoglu, et al. (2004). "Selenium and high dose vitamin E administration protects cisplatin-induced oxidative damage to renal, liver and lens tissues in rats." Toxicology **195**(2-3): 221-30.

Cisplatin is one of the most active cytotoxic agents in the treatment of cancer but its clinical use is associated with nephrotoxicity. Several studies suggest that supplementation with antioxidant can influence cisplatin induced nephrotoxicity. In the present study, we investigated the effect of selenium with high dose vitamin E administration on lipid peroxidation (MDA) and scavenging enzyme activity in kidneys, liver and lens of cisplatin-induced toxicity in rats. Forty female Wistar rats were used. They were randomly divided into five groups. The first and second groups were used as control and cisplatin (6 mg/kg BW) intraperitoneally administrated groups. Groups III, IV and V received intraperitoneally five doses of selenium (1.5 mg/kg BW) and a high dose of vitamin E (1000 mg/kg BW) combination before, simultaneously and after with cisplatin, respectively. Glutathione peroxidase (GSH-Px), vitamin E and beta-carotene levels in the kidney, lens and liver, vitamin A and reduced glutathione (GSH) levels in the kidney were significantly ($P<0.05$ to <0.001) lower in the cisplatin group than in the control whereas there was a significant increase in kidney, liver and lens MDA levels in rats treated with cisplatin. The decreased antioxidant enzymes and vitamins and

increased MDA levels in the kidney, lens and liver of animals administered with cisplatin were significantly (P<0.05 to <0.001) improved with selenium and a high dose vitamin E injection. In conclusion, this data demonstrates that there is an increase in lipid peroxidation in the kidney, liver and lens of animals administered with cisplatin whereas there is a decrease in antioxidant vitamins and enzymes. However, intraperitoneally injected selenium combined with a high dose of vitamin E seem to produce a significant improvement on antioxidants concentrations in rats treated before, simultaneously and after with cisplatin. The selenium with high dose vitamin E injection may play a role in preventing cisplatin-induced nephropathy and cataract formation in cancer patient.

Sarna, S., A. Kumar, et al. (2000). "alpha-Tocopherol enhances tumour growth inhibition by cis-dichlorodiammine platinum (II)." Braz J Med Biol Res **33**(8): 929-36.

Present studies indicate that alpha-tocopherol enhances the efficacy of cisplatin as demonstrated by inoculation of Dalton's lymphoma cells incubated with either cisplatin (5 or 10 microg/ml) alone or cisplatin + alpha-tocopherol (25 or 50 microg/ml) into C3H/He mice. Tumour cells (3 x 10(6) cells/mouse) incubated with cisplatin grow slowly in syngeneic mice as indicated by the late appearance of tumour. However, mice failed to develop tumour when inoculated with tumour cells incubated with cisplatin + alpha-tocopherol. When the animals were challenged with tumour cells (3 x 10(6) cells/mouse) on the 15th day after the initial inoculation, 30-50% survived more than 60 days, with 10% tumour-free survivors being observed in some groups. Antitumour activity was higher in mice receiving lymphoma cells (3 x 10(6) cells/mouse) preincubated with cisplatin + alpha-tocopherol compared to cisplatin alone. Tumour-bearing mice receiving cisplatin in combination with different concentrations of alpha-tocopherol exhibited significantly higher (P<0.001) intratumour platinum content (123-306%) but without any change in the kidney platinum content as compared to those receiving cisplatin (5 or 10 microg/ml) alone. Enhancement of cisplatin-induced tumour growth inhibition is probably due to the modulation of tumour cell membrane permeability by alpha-tocopherol. alpha-Tocopherol might increase the influx of cisplatin into tumour cells, causing the DNA repair machinery to be less efficient due to increased efficiency of adduct formation in the DNA molecule. This effect of alpha-tocopherol can render cisplatin more effective as an antitumour agent.

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.

Sue, K., A. Nakagawara, et al. (1988). "Combined effects of vitamin E (alpha-tocopherol) and cisplatin on the growth of murine neuroblastoma in vivo." Eur J Cancer Clin Oncol **24**(11): 1751-8.

Combined effects of vitamin E (alpha-tocopherol) and cisplatin on the growth of two murine neuroblastomas (C1300, NS-20) was investigated in vivo. Five groups of mice were prepared; group 1 were fed the control diet, group 2 were fed a vitamin E-deficient diet, group 3 were fed a vitamin E-supplemented diet, group 4 were fed the control diet and plus vitamin E solution given intraperitoneally during the treatment (solvent i.p. group), and group 5 were given vitamin E in the same manner (20 mg/kg/day; vitamin E i.p. group). Cisplatin (6 mg/kg) was injected intraperitoneally into the mice of each group during the treatment. In case of the C1300 neuroblastoma, the antitumor activity of cisplatin was most enhanced in the mice receiving vitamin E i.p., and the intra-tumor vitamin E and platinum levels were significantly higher in this group than in the other groups (P less than 0.01, and P less than 0.05 respectively). In contrast, in animals transplanted with the NS-20 murine neuroblastoma, which proved

to be a cisplatin-tolerant tumor in separate experiments, no combined effect of those drugs was observed, although the intra-tumor level of platinum was elevated. The possibility was that vitamin E increases the influx of cisplatin into the tumor cells and acts after incorporation of cisplatin through the plasma membrane. Vitamin E did not accentuate the cisplatin-induced renal impairment in vitamin E-loaded groups. Those results suggested that vitamin E should be considered as a co-agent of cisplatin for the treatment of neuroblastoma.

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.