

Cancer: Should Patients Take Dietary Supplements?

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## ABSTRACTS

Stromal cell oxidation: a mechanism by which tumors obtain vitamin C.

Agus DB, Vera JC, Golde DW.

*Cancer Res.* 1999 Sep 15; 59(18):4555-8.

Human tumors may contain high concentrations of ascorbic acid, but little is known about how they acquire the vitamin. Certain specialized cells can transport ascorbic acid directly through a sodium ascorbate cotransporter, but in most cells, vitamin C enters through the facilitative glucose transporters (GLUTs) in the form of dehydroascorbic acid, which is then reduced intracellularly and retained as ascorbic acid. Mice with established hematopoietic and epithelial cell xenografts were studied for the accumulation of injected ascorbic acid and dehydroascorbic acid. Most hematopoietic and epithelial tumor cell lines can only transport vitamin C in the oxidized form (dehydroascorbic acid) in vitro; however, when grown as xenografts in mice, they rapidly accumulated vitamin C after administration of radiolabeled ascorbic acid. The involvement of the GLUTs in vitamin C uptake by the xenografted tumors was demonstrated by competitive inhibition with D-glucose but not L-glucose. Because the malignant cells were not capable of directly transporting ascorbic acid, we reasoned that the ascorbic acid was oxidized to dehydroascorbic acid in the tumor microenvironment. Tumor accumulation of vitamin C in animals injected with ascorbic acid was inhibited by coadministration of superoxide dismutase, implying a role for superoxide anion in the oxidation of ascorbic acid. Whereas the epithelial cancer cell lines could not generate superoxide anion in culture, the minced xenograft tumors did. Our studies show the transport of dehydroascorbic acid by GLUTs is a means by which tumors acquire vitamin C and indicate the oxidation of ascorbic acid by superoxide anion produced by cells in the tumor stroma as a mechanism for generating the transportable form of the vitamin.

Comparative study of doxorubicin, mitoxantrone, and epirubicin in combination with ICRF-187 (ADR-529) in a chronic cardiotoxicity animal model.

Alderton PM, Gross J, Green MD.

*Cancer Res.* 1992 Jan 1; 52(1):194-201.

In this study doxorubicin, epirubicin, and mitoxantrone were compared for their cardiotoxic potential in a chronic mouse model in an effort to identify and compare their mechanism(s) of toxicity. In addition, the cardioprotective ability of ICRF-187 [(+/-)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane] with each anticancer drug was evaluated in this model. The antioxidant capacity (superoxide dismutase, reduced glutathione, catalase, and glutathione peroxidase) was assessed following drug treatment. Five-week-old BALB/c mice received weekly i.p. injections of each drug or the drug and ICRF-187 over a 3-month period. ICRF-187 was administered 30 min prior to the anticancer drug. The hearts were examined by electron and light microscopy to assess subcellular changes, and the cardiac and hepatic antioxidant levels were measured concurrently. Chronic treatment with these drugs or each combined with ICRF-187 did not change the antioxidant levels relative to the control values. However, all three drugs caused cardiac damage during chronic exposure. Both epirubicin and mitoxantrone caused less severe damage than doxorubicin, and epirubicin was the least cardiotoxic of the three. ICRF-187 was cardioprotective for epirubicin and doxorubicin but not for mitoxantrone. These results suggest epirubicin acts by a mechanism similar to that of doxorubicin that is probably mediated by oxygen-free radicals, while mitoxantrone acts by a different mechanism to cause cardiotoxicity.

Serum folate and homocysteine levels in head and neck squamous cell carcinoma.

Almadori G, Bussu F, Galli J, et al.

*Cancer.* 2002 Feb 15; 94(4):1006-11.

**BACKGROUND:** Local and systemic metabolic alterations are always present in cancer. Carcinogenesis is associated with biochemical disorders, often nonspecific, that might promote or derive from tumoral progression. Thus, analysis of metabolic alterations may be a valuable approach to understanding the biochemistry of tumors and may provide a means of identifying new

targets for therapy. The methionine cycle in particular has been extensively studied in human cancer. METHODS: The authors analyzed serum concentrations of two metabolites of such pathways, folate and homocysteine, in 42 patients affected by head and neck squamous cell carcinoma (HNSCC) in comparison with two control groups, composed of smokers and non smokers. RESULTS: Mean folate level was 5.8 +/- 2.1 ng/mL in carcinoma patients, 9.1 +/- 2.7 ng/mL in smoking controls, and 9.7 +/- 2.2 ng/mL in non smoking controls, with a statistically significant difference between carcinoma patients and smokers (mean difference: -3.3 ng/mL; 95% confidence interval [CI]: -4.234 to -2.366; P < 0.0001) and between carcinoma patients and non smokers (mean difference: -3.9 ng/mL; 95% CI: -4.67 to -3.13; P < 0.0001). Mean total homocysteine level was 10.4 +/- 5.3 microM in carcinoma patients, 7.8 +/- 2.5 microM in the non-smokers' group, and 8.3 +/- 2.8 microM in the smokers' group, with statistically significant differences between carcinoma patients and smoking controls (mean difference: 2.1 microM; 95% CI: 0.7056 to 3.494; P = "0.0034") and between carcinoma patients and non smoking controls (mean difference: 2.6 microM; 95% CI: 1.381 to 3.819; P < 0.0001). CONCLUSIONS: Differences in serum levels of folate and homocysteine might arise from tumor development and consequent metabolic alterations or might precede and promote tumor progression. If hypofolatemia is a risk factor for head and neck carcinogenesis, it might suggest a role for folate as a novel chemopreventive agent both in patients with precancerous lesions and in patients with treated HNSCC at risk for loco-regional recurrence and second primary tumors

Retinoic acid treatment of human neuroblastoma cells is associated with decreased N-myc expression.

Amatruda TT, III, Sidell N, Ranyard J, et al.

*Biochem Biophys Res Commun.* 1985 Feb 15; 126(3):1189-95.

Cells from human neuroectodermal tumors (retinoblastoma and neuroblastoma) and from neuroblastoma cell lines express a gene, N-myc, which is frequently amplified in these tumors. We report here that N-myc mRNA content is markedly decreased in cells of a neuroblastoma cell line (LA-N-5) following differentiation induced with retinoic acid. Exposure of the cells to retinoic acid induced morphologic changes consistent with neuronal differentiation, and led to a 75% decrease in expression of N-myc mRNA. These results suggest that N-myc expression is intimately related to an undifferentiated phenotype in neuroblastoma cells, and support other studies which relate N-myc expression to the malignant phenotype in neuroblastoma tumors

[Effect of thioctic acid (alpha-limpoic acid) on the chemotherapeutic efficacy of cyclophosphamide and vincristine sulfate].

Berger M, Habs M, Schmahl D.

*Arzneimittelforschung.* 1983; 33(9):1286-8.

Pretreatment with thioctic acid has no negative influence on the chemotherapeutic efficacy of cyclophosphamide against i.p. transplanted Yoshida sarcoma and vincristine sulfate against i.p. transplanted Walker carcinosarcoma 256. The toxic side effects of vincristine sulfate are lowered to such a degree that an increase results in median survival time compared to animals treated only with vincristine sulfate. A diminution of the toxic side effects of cyclophosphamide due to adjuvant treatment with thioctic acid could not be proven

Circadian rhythms in antioxidant dosing following chemotherapy.

Bland J.

1999;Jun

Nutrition and cancer-scientific basis and clinical applications. Presented at Comprehensive Cancer Care 2001, ; see also Bland J., Lord, S., Smith, K. Nutritional support for cancer patients: a basic program. Presented at Comprehensive Cancer Care 2001, Arlington , VA , October 19-21, 2001.

Bland J.

2001;Arlington, VA, October 19-21, 2001;

Creating an Integrative Program of Cancer Care. Comprehensive Cancer Care 2001.

Block K.

2001;

Anti-oxidant vitamins reduce normal tissue toxicity induced by radio-immunotherapy.

Blumenthal RD, Lew W, Reising A, et al.

*Int J Cancer.* 2000 Apr 15; 86(2):276-80.

Our purpose was to determine whether the administration of anti-oxidant vitamins could reduce dose-limiting toxicity from radio-immunotherapy (RAIT) and thereby allow higher escalation of RAIT doses. Lipophilic vitamins A and E were administered i.p. and hydrophilic vitamin C was administered i.m. for 14 days (3 days pre-RAIT through 11 days post-RAIT) alone or with bone marrow transplantation (BMT) to either BALB/c mice for toxicity studies or to nude mice bearing s.c. GW-39 human colonic cancer xenografts for therapy studies. The maximal tolerated dose (MTD) of RAIT ((131)I-MN14 anti-CEA IgG) that results in no lethality was determined for mice that did not receive vitamins or BMT and those that did receive one or both interventions. Body weight, peripheral white blood cell (pWBC) and platelet (PLT) counts and tumor growth were also measured. Administration of vitamins (equivalent of 3.5 IU/day vitamin A, 0.107 IU/day vitamin E and 4.0 mg/day ascorbic acid) to mice along with BMT increased the MTD by 42% and reduced body weight loss associated with RAIT. Vitamins also reduced the magnitude of RAIT-induced myelosuppression. As early as day 7 after RAIT, vitamins increased WBC counts following both a 400 microCi and a 500 microCi dose. On day 14 after the 400 microCi dose of RAIT (day 7 post-BMT), the additive effect of BMT and vitamin could be detected. Tumor growth was not adversely affected by vitamin administration

Influence of tangeretin on tamoxifen's therapeutic benefit in mammary cancer.

Bracke ME, Depypere HT, Boterberg T, et al.

*J Natl Cancer Inst.* 1999 Feb 17; 91(4):354-9.

**BACKGROUND:** Tamoxifen and the citrus flavonoid tangeretin exhibit similar inhibitory effects on the growth and invasive properties of human mammary cancer cells in vitro; furthermore, the two agents have displayed additive effects in vitro. In this study, we examined whether tangeretin would enhance tamoxifen's therapeutic benefit in vivo. **METHODS:** Female nude mice (n = 80) were inoculated subcutaneously with human MCF-7/6 mammary adenocarcinoma cells. Groups of 20 mice were treated orally by adding the following substances to their drinking water: tamoxifen ( $3 \times 10^{-5}$  M), tangeretin ( $1 \times 10^{-4}$  M), tamoxifen plus tangeretin ( $3 \times 10^{-5}$  M plus  $1 \times 10^{-4}$  M), or solvent. **RESULTS AND CONCLUSIONS:** Oral treatment of mice with tamoxifen resulted in a statistically significant inhibition of tumor growth compared with solvent treatment (two-sided  $P = .001$ ). Treatment with tangeretin did not inhibit tumor growth, and addition of this compound to drinking water with tamoxifen completely neutralized tamoxifen's inhibitory effect. The median survival time of tumor-bearing mice treated with tamoxifen plus tangeretin was reduced in comparison with that of mice treated with tamoxifen alone (14 versus 56 weeks; two-sided  $P = .002$ ). Tangeretin ( $1 \times 10^{-6}$  M or higher) inhibited the cytolytic effect of murine natural killer cells on MCF-7/6 cells in vitro, which may explain why tamoxifen-induced inhibition of tumor growth in mice is abolished when tangeretin is present in drinking water. **IMPLICATIONS:** We describe an in vivo model to study potential interference of dietary compounds, such as flavonoids, with tamoxifen, which could lead to reduced efficacy of adjuvant therapy. In our study, the tumor growth-inhibiting effect of oral tamoxifen was reversed upon addition of tangeretin to the diet. Our data argue against excessive consumption of tangeretin-added products and supplements by patients with mammary cancer during tamoxifen treatment

Nutritional folate status influences the efficacy and toxicity of chemotherapy in rats.

Branda RF, Nigels E, Lafayette AR, et al.

*Blood.* 1998 Oct 1; 92(7):2471-6.

The effect of folate status on the efficacy and toxicity of chemotherapy was investigated in weanling Fischer 344 rats maintained on diets of varying folate content or supplemented with daily injections of folic acid, 50 mg/kg, for 6 to 7 weeks. MADB106 rat mammary tumor growth rate was the same in folate replete and supplemented rats, but retarded in the low folate groups. The tumor growth inhibitions in low folate, replete and high folate rats treated with cyclophosphamide were: 53%, 98%, and 97% ( $P = .048$ ); with 5-fluorouracil (5-FU): 46%, 49%, and 66%; and with doxorubicin: 25%, 55%, and 61%. Significant differences in survival were observed for cyclophosphamide ( $P = .0084$ ) and 5-FU ( $P = .025$ ) related to dietary folate content. Thus, folate deficiency impedes tumor growth rate, but supplementation does not accelerate it in folate replete animals. Correction of folate deficiency approximately doubles the efficacy of cyclophosphamide in rats with much less host toxicity. Folate repletion improves survival in 5-FU-treated animals. These studies indicate that nutritional folate status has an important influence on the efficacy and toxicity of some commonly used cancer chemotherapeutic drugs

Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, ifosfamide, trofosfamide and sufosfamide.

Brock N, Stekar J, Pohl J, et al.

*Arzneimittelforschung*. 1979; 29(4):659-61.

The urotoxicity of oxazaphosphorine cytostatics is not based on their alkylating activity but on the presence of acrolein, which is spontaneously formed in the urine from the primary metabolites eliminated via the kidneys. Thus, acrolein proved to be the causative factor in the urotoxicity of oxazaphosphorines. The mechanism of action of the uroprotector sodium 2-mercaptoethane-sulfonate (mesnum, Mitexan) is mainly based on the formation of a non-toxic additive compound with acrolein

Molecular detection of prostate cancer in urine by GSTP1 hypermethylation.

Cairns P, Esteller M, Herman JG, et al.

*Clin Cancer Res*. 2001 Sep; 7(9):2727-30.

Novel approaches for the early detection and management of prostate cancer are urgently needed. Clonal genetic alterations have been used as targets for the detection of neoplastic cells in bodily fluids from many cancer types. A similar strategy for molecular diagnosis of prostate cancer requires a common and/or early genetic alteration as a specific target for neoplastic prostate cells. Hypermethylation of regulatory sequences at the glutathione S-transferase pi (GSTP1) gene locus is found in the majority (>90%) of primary prostate carcinomas, but not in normal prostatic tissue or other normal tissues. We hypothesized that urine from prostate cancer patients might contain shed neoplastic cells or debris amenable to DNA analysis. Matched specimens of primary tumor, peripheral blood lymphocytes (normal control), and simple voided urine were collected from 28 patients with prostate cancer of a clinical stage amenable to cure. Genomic DNA was isolated from the samples, and the methylation status of GSTP1 was examined in a blinded manner using methylation-specific PCR. Decoding of the results revealed that 22 of 28 (79%) prostate tumors were positive for GSTP1 methylation. In 6 of 22 (27%) cases, the corresponding urine-sediment DNA was positive for GSTP1 methylation, indicating the presence of neoplastic DNA in the urine. Furthermore, there was no case where urine-sediment DNA harbored methylation when the corresponding tumor was negative. Although we only detected GSTP1 methylation in under one-third of voided urine samples, we have demonstrated that molecular diagnosis of prostate neoplasia in urine is feasible. Larger studies focusing on carcinoma size, location in the prostate, and urine collection techniques, as well as more sensitive technology, may lead to the useful application of GSTP1 hypermethylation in prostate cancer diagnosis and management

Ascorbic acid and cancer: a review.

Cameron E, Pauling L, Leibovitz B.

*Cancer Res*. 1979 Mar; 39(3):663-81.

Host resistance to neoplastic growth and invasiveness is recognized to be an important factor in determining the occurrence, the progress, and the eventual outcome of every cancer illness. The factors involved in host resistance are briefly reviewed, and the relationship between these factors and ascorbic acid metabolism is presented in detail. It is shown that many factors involved in host resistance to neoplasia are significantly dependent upon the availability of ascorbate

Effects of retinoic acid on cell differentiation and reversion toward normal in human endometrial adenocarcinoma (RL95-2) cells.

Carter CA, Pogribny M, Davidson A, et al.

*Anticancer Res*. 1996 Jan; 16(1):17-24.

**BACKGROUND:** All-trans retinoic acid is currently used in clinical trials in combination with tamoxifen to treat breast cancer, and 13-cis retinoic acid is used with  $\alpha$ -interferon to treat metastatic endometrial cancer. We examined the effects of all-trans retinoic acid and 13-cis RA alone on endometrial adenocarcinoma (RL95-2) cells to investigate the cell biological mechanisms by which retinoic acid may reduce the metastatic phenotype and induce differentiation. **METHODS:** RL95-2 cells were seeded onto 4-chamber plastic slides and treated with 13-cis retinoic acid or all-trans retinoic at 0.5  $\mu$ M, 1  $\mu$ M and 5  $\mu$ M doses for 90 minutes at 37 degrees C and stained for F-actin. **RESULTS:** Untreated RL95-2 cells exhibited staining of disrupted aggregates of F-actin only near the cell periphery. Cells treated with the three doses of 13-cis retinoic acid exhibited a dramatic reorganization of F-actin throughout the cells. When cells were treated with 0.5  $\mu$ M all-trans retinoic acid, actin filaments reorganized. Cells treated with 1  $\mu$ M all-trans retinoic acid and 5  $\mu$ M all-trans retinoic acid displayed increased organization of F-actin and cell size increased. The percentage of S-phase cells increased at the high doses of retinoic acid treatment. This effect was apparently transient, since retinoic acid did not significantly affect cell growth. **CONCLUSION:** An organized cytoskeleton and an increase in cell size are associated with differentiation. We suggest that retinoic acid exerts its effects on these transformed cells by reorganizing actin filaments, and inducing differentiation, thus inducing a more stationary phenotype

Genetic events associated with arsenic-induced malignant transformation: applications of cDNA microarray technology.

Chen H, Liu J, Merrick BA, et al.

*Mol Carcinog.* 2001 Feb; 30(2):79-87.

Arsenic is a human carcinogen. Our recent work showed that chronic (>18 wk), low-level (125-500 nM) arsenite exposure induces malignant transformation in normal rat liver cell line TRL1215. In these arsenic-transformed cells, the cellular S-adenosylmethionine pool was depleted from arsenic metabolism, resulting in global DNA hypomethylation. DNA methylation status in turn may affect the expression of a variety of genes. This study examined the aberrant gene expression associated with arsenic-induced transformation with the use of Atlas Rat cDNA Expression microarrays. Poly(A(+)) RNA was prepared from arsenic-transformed cells and passage-matched control cells, and (32)P-labeled cDNA probes were synthesized with Clontech Rat cDNA Synthesis primers and moloney murine leukemia virus reverse transcriptase. The hybrid intensity was analyzed with AtlasImage software and normalized with the sum of the four housekeeping genes. Four hybridizations from separate cell preparations were performed, and mean and SEM for the expression of each gene were calculated for statistical analysis. Among the 588 genes, approximately 80 genes (approximately 13%) were aberrantly expressed. These included genes involved in cell-cycle regulation, signal transduction, stress response, apoptosis, cytokine production and growth-factor and hormone-receptor production and various oncogenes. These initial gene expression analyses for the first time showed potentially important aberrant gene expression patterns associated with arsenic-induced malignant transformation and set the stage for numerous further studies. *Mol. Carcinog.* 30:79-87, 2001. Published 2001 Wiley-Liss, Inc

Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer: a p53-independent induction of p21WAF1/CIP1 via C/EBPbeta.

Chinery R, Brockman JA, Peeler MO, et al.

*Nat Med.* 1997 Nov; 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

Ascorbic acid and gastrointestinal cancer.

Cohen M, Bhagavan HN.

*J Am Coll Nutr.* 1995 Dec; 14(6):565-78.

A literature review was made to critically evaluate the ability of ascorbic acid to modulate the incidence of gastrointestinal cancer. A comparison of preclinical, clinical, and epidemiological studies indicated that evidence for ascorbic acid as an inhibitor of carcinogenesis is stronger with regard to gastric cancer and weaker with regard to esophageal and colon/rectal cancer. Insufficient evidence currently exists regarding the oral cavity and the use of ascorbic acid in precancerous conditions such as polyposis and leukoplakia

Contrasting effects of vitamins as modulators of apoptosis in cancer cells and normal cells: a review.

Cole WC, Prasad KN.

*Nutr Cancer.* 1997; 29(2):97-103.

Individual vitamins can induce direct apoptosis or indirect apoptosis via cell differentiation in cancer cells; however, they can also stimulate antiapoptotic events in certain cancer cells. These effects depend on the dose, type, and form of vitamins and the type of tumor cells. A mixture of antioxidant vitamins is more effective than individual vitamins, and there is no evidence that such a mixture ever stimulates antiapoptotic events in cancer cells. Vitamins in combination with nonvitamin, direct-acting, apoptotic agents (X-rays, chemotherapeutic agents, and hyperthermia) or in combination with nonvitamin, indirect-acting, apoptotic agents (adenosine 3',5'-cyclic monophosphate, butyric acid, and interferon) produce a greater extent of apoptotic death in cancer cells

in culture. Certain antioxidant vitamins may reduce the efficacy of some chemotherapeutic agents on rodent fibrosarcoma cells. In contrast to vitamin-induced apoptosis in cancer cells, normal cells never undergo apoptotic death after treatment with vitamins (not including retinoids). On the contrary, vitamins protect normal cells against apoptosis induced by a certain group of chemicals. The reasons for this differential effect of vitamins on cancer and normal cells are unknown. The genetic regulation of apoptosis in cancer cells has not been adequately defined. Such studies would help in identifying molecular targets that can be used to develop effective doses of vitamins or new drugs to induce apoptosis selectively in cancer cells

13-cis-retinoic acid with alpha-2a-interferon enhances radiation cytotoxicity in head and neck squamous cell carcinoma in vitro.

Delaney TF, Afridi N, Taghian AG, et al.

*Cancer Res.* 1996 May 15; 56(10):2277-80.

The treatment of locally advanced squamous cell carcinomas of the head and neck presents a challenge for oncologists. Radiation therapy alone fails to control many of these tumors. Chemotherapy added to radiation therapy has not clearly demonstrated an improvement in survival in the majority of trials reported to date. In this study, we have evaluated whether IFN-alpha-2a and/or 13-cis-retinoic acid (RA) enhance radiation cytotoxicity in a head and neck squamous cell carcinoma cell line (FaDu). Using a clonogenic cell survival assay, IFN-alpha-2a (1000 units/ml) or RA (1 microM) alone did not significantly enhance radiation cytotoxicity. The combination of the two agents, however, significantly increased the cytotoxicity of radiation against FaDu cells. The calculated survival fraction at 2 Gy was decreased from 0.649 with radiation alone to 0.477 when combined with the other two agents ( $P = 0.016$ ), and the MID was decreased from 3.318 to 2.499 Gy ( $P = 0.028$ ). A Phase I clinical trial to combine IFN-alpha-2a and/or RA in patients with unresectable head and neck cancer has been initiated

Combined effect of lipoic acid and doxorubicin in murine leukemia.

Dovinova I, Novotny L, Rauko P, et al.

*Neoplasma.* 1999; 46(4):237-41.

Our experiments indicate that administration of a toxic drug with high rate of free-radical formation (doxorubicin, DOX) combined with an antioxidant (alpha-lipoic acid, LA) may lead to a decrease in drug-toxicity. However, the effects of antioxidant may be concentration-dependent and it is therefore crucial to choose its appropriate dosage. LA at a low concentration (1 micromol/l) acts as a growth factor and at a higher concentration (100 micromol/l) acts as an antiproliferation agent. Both concentrations of LA in combination with DOX were examined in cytotoxic and antitumor effects in L1210 mouse leukemia cells employing a MTT chemosensitivity assay. In most concentration combinations, DOX and LA effect were antagonistic and synergistic action was only found at the higher concentration of both agents (DOX 2.5 micromol/l and LA 100 micromol/l). Use of LA in doxorubicin therapy lead to an increase (though marginally significant) in survival of animals. Combined single-dose administration of DOX (5 mg/kg) and LA (16 mg/kg) lead to super-additive effect of the combination on survival of leukemic mice

Roferon-A (interferon alpha 2a) combined with Tigason (etretinate) for treatment of cutaneous T cell lymphomas.

Dreno B.

*Stem Cells.* 1993 Jul; 11(4):269-75.

Many treatments are used for epidermotropic cutaneous T cell lymphomas (CTCL) such as mycosis fungoides (MF) and Sezary syndrome (SS). All pretend to be effective, but none is really curative. As single drug therapy provides a response rate of about 55% with interferon alpha and about 45% with etretinate, we studied the effectiveness of combining these two drugs for immunomodulatory therapy in epidermotropic CTCL. A review of four reports, including a multicenter study performed in 45 patients, indicates a response rate of 56%, with better results for MF than SS. Side effects are generally moderate when low doses are used. The mechanism of action of this combined therapy on cutaneous lesions remains unclear. In vitro, a synergistic effect of retinoids on interferon alpha antiviral activity has been demonstrated, and in vivo an immunohistochemical study showed that the combined therapy modulates antigens expressed by keratinocytes and increases cytotoxic cells in dermis without modifying the number of Langerhans cells in epidermis

Recommended dietary allowances (RDAs) for genomic stability.

Fenech M.

*Mutat Res.* 2001 Sep 1; 480-481:51-4.

Diet as a key factor in determining genomic stability is more important than previously imagined because we now know it impacts on all relevant pathways, i.e. exposure to dietary carcinogens, activation/detoxification of carcinogens, DNA repair, DNA synthesis and apoptosis. Current recommended dietary allowances for vitamins and minerals are based largely on the prevention of diseases of deficiency such as scurvy in the case of Vitamin C. Because diseases of development, degenerative disease and ageing itself are partly caused by damage to DNA, it seems logical that we should focus better our attention on defining optimal requirements of key minerals and vitamins for preventing damage to both nuclear and mitochondrial DNA. To date our knowledge on optimal micronutrient levels for genomic stability is scanty and disorganised. Appropriately designed placebo, controlled trials are required to define recommended dietary allowances for genomic stability. Recently, it has been shown that above RDA intakes of folic acid and Vitamin B12 are required to reduce the micronucleus index in humans by 25%. In the future, clinical trials with a defined wider array of complementary DNA damage end-points would be necessary. That there is a need for an international collaborative group to establish RDAs for genomic stability is self-evident and this paper is a call for such a process to begin

Beta-carotene and antioxidant nutrients in oral cancer prevention. In *Nutrients in Cancer Prevention and Treatment* 1995.

Garewal H.

1995;235-47.

DNA-based detection of prostate cancer in blood, urine, and ejaculates.

Goessl C, Muller M, Heicappell R, et al.

*Ann N Y Acad Sci.* 2001 Sep; 945:51-8.

**BACKGROUND:** Methylation-specific polymerase chain reaction (MSP) targeting promoter hypermethylation of the glutathione S transferase P1 gene (GSTP1), as the most frequent DNA alteration in prostatic carcinoma, was used for the molecular detection of cell-bound and cell-free prostate tumor DNA in various human bodily fluids. **MATERIALS AND METHODS:** We investigated GSTP1 promoter hypermethylation in DNA isolated from plasma, serum, nucleated blood cells, ejaculates, urines after prostate massage, and prostate tissue from 33 patients with prostate cancer and 26 control patients with benign prostatic hyperplasia (BPH). Using a viral DNA extraction kit specifically recommended for DNA isolation from urine samples, GSTP1 promoter hypermethylation in urine sediments after prostatic massage was investigated in a cohort of 29 patients with prostate cancer and 40 controls with BPH. Fluorescently labeled MSP products were analyzed on an automated gene sequencer. **RESULTS:** GSTP1 promoter hypermethylation was found in 90% of tumors (18 of 20), 72% of plasma or serum samples (23 of 32), 50% of ejaculates (4 of 8), and between 36% (4 of 11; normal DNA isolation kit) and 76% (22 of 29; viral kit) of exprimated urines from patients with prostate cancer. Also, MSP identified circulating tumor cells in 30% (10 out of 33) of prostate cancer patients. Except for one urine sample, GSTP1 promoter hypermethylation was not found in tissue and body fluids from patients with BPH. **CONCLUSION:** GSTP1 promoter methylation analysis provides a highly specific tool for DNA-based diagnosis of prostate cancer in body fluids

Beta-carotene induces morphological differentiation and decreases adenylate cyclase activity in melanoma cells in culture.

Hazuka MB, Edwards-Prasad J, Newman F, et al.

*J Am Coll Nutr.* 1990 Apr; 9(2):143-9.

Several studies suggest that beta-carotene reduces the risk of some cancers. Except for its function as an antioxidant, the effect of this vitamin on mammalian cells remains poorly defined. This study was performed to show whether beta-carotene treatment of murine B-16 melanoma cells in culture induces differentiation and alters the adenylate cyclase (AC) system. The AC system mediates the action of agents which regulate cell differentiation and transformation. Results showed that beta-carotene treatment for a period of 24 hours or more caused morphological differentiation without changing the level of melanin, and reduced basal and melanocyte-stimulated hormone (MSH)-, sodium fluoride (NaF)-, and forskolin-stimulated AC activity in vitro. Retinol, a metabolite of beta-carotene, inhibited growth without morphological differentiation and reduced basal and MSH- and NaF-stimulated AC activity. However, butylated hydroxyanisole, a lipid-soluble antioxidant, also reduced growth without morphological differentiation, but it failed to alter basal or MSH-stimulated AC activity. The present and previous studies show that the AC system represents a common site where some antitumor-promoting vitamins (beta-carotene, retinol, retinoic acid, and alpha-tocopheryl succinate) act

[Asymmetry and mutuality in the analytic relationship: lessons for today from the relationship between Freud and Ferenczi].

Hoffer A.

*Psyche (Stuttg)*. 1993 Nov; 47(11):1027-40.

Against the background of the controversy between Freud and Ferenczi on the nature of the psychoanalytic relationship, Hoffer examines the perennial issue of the way in which analysts come to terms with the warring claims of asymmetry (Freud) and mutuality (Ferenczi) in analysis. While discerning an inherent tendency towards mutuality in the psychoanalytic constellation, the author nevertheless calls for the upholding of asymmetry because the psychoanalytic relationship is not a relationship "of the usual kind". The analyst, he contends, must sustain the tension between mutuality and asymmetry and use this reflected tension as a therapeutic instrument for fathoming the patient's psychic reality

Isoniazid and pyridoxine.

Hoffer A.

*CMAJ*. 1993 Nov 1; 149(9):1232.

Dioxin induces transcription of fos and jun genes by Ah receptor-dependent and -independent pathways.

Hoffer A, Chang CY, Puga A.

*Toxicol Appl Pharmacol*. 1996 Nov; 141(1):238-47.

Halogenated aromatic hydrocarbons, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; dioxin), and polycyclic aromatic hydrocarbons, such as benzo[a]pyrene, are environmental contaminants that cause many apparently unrelated toxic effects. In a previous study, we have shown that treatment of mouse hepatoma cells with TCDD or B(a)P results in an increase in mRNA levels of the immediate-early protooncogenes c-fos, c-jun, junB, and junD, and the concomitant increase of the DNA-binding activity of the transcription factor AP-1, a dimer of FOS and JUN proteins. To analyze the mechanism of fos/jun activation by TCDD we have used electrophoretic mobility shift and transient expression assays of reporter gene constructs containing response elements for 12-O-tetradecanoyl-phorbol-13-acetate (TRE), serum (SRE), cAMP (CRE), and aromatic hydrocarbons (AhRE) from the fos and jun genes fused to the firefly luciferase gene under the control of the SV40 minimal promoter. In mouse hepatoma Hepa-1 cells, which have Ah receptor (AHR) and Ah receptor nuclear translocator (ARNT) proteins, inclusion of TRE, SRE, and the AhRE motifs from c-jun and junD, but not CRE or the AhREs from c-fos, fosB, and junB, causes a large TCDD-dependent increase in luciferase expression. In agreement with these results, c-jun and junD, but not c-fos, fosB, and junB AhREs, competed with a canonical Cyp1A1 AhRE for binding to the AHR ARNT heterodimeric complex. In African Green Monkey CV-1 cells, which lack AHR, expression plasmids with AhRE motifs require coexpression of AHR and ARNT for TCDD to stimulate luciferase expression. In contrast, SRE-containing expression plasmids respond equally well to TCDD whether or not AHR and ARNT are coexpressed. These results suggest that TCDD induces expression of the immediate-early response genes fos and jun by activation of possibly three separate signal transduction pathways, at least one of which does not require a functional Ah receptor complex

One patient's recovery from lymphoma. *Townsend Letter for Doctors and Patients*.

Hoffer A.

1996 160:50-1.

Hardin Jones biostatistical analysis of morality data for cohorts of cancer patients with a large fraction surviving at the termination of the study and a comparison of survival times of cancer patients receiving large regular oral doses of vitamin C and other nutrients with similar patients not receiving those doses. - reprinted in Cameron, E., Pauling, L. *Cancer and Vitamin C*.

Hoffer APL.

*J Orthomol Med*. 1993;(5):143-54-199.

Hardin Jones biostatistical analysis of mortality data for a second set of cohorts of cancer patients with a large fraction surviving at the termination of the study and a comparison of survival time of cancer patients receiving large regular oral doses of vitamin C and other nutrients with similar patients not receiving these doses.

Hoffer APL.

*J Orthomol Med*. 1993;(8):1547-67.

Vitamin E succinate induces apoptosis in human prostate cancer cells: role for Fas in vitamin E succinate-triggered apoptosis.

Israel K, Yu W, Sanders BG, et al.

*Nutr Cancer*. 2000; 36(1):90-100.

The apoptosis-triggering properties of vitamin E succinate (VES, RRR-alpha-tocopheryl succinate) for human LNCaP and PC-3 prostate carcinoma cells and normal PrEC human prostate epithelial cells were investigated. LNCaP and PC-3 cells were sensitive to VES-induced apoptosis, with 100% and 60% of cells undergoing apoptosis after three days of treatment with 10 micrograms of VES/ml, respectively. PrEC cells were resistant to VES-induced apoptosis. Treatment of prostate cells with agonistic anti-Fas antibody triggered apoptosis in approximately 50% of PC-3 cells within 48 hours, whereas LNCaP and PrEC cells were resistant. Prostate cells simultaneously treated with VES and agonistic anti-Fas antibodies revealed 1) no effect on PrEC cells, 2) an additive effect on Fas-sensitive PC-3 cells, and 3) a synergistic effect on LNCaP cells. VES treatment of LNCaP cells caused depletion of cytosolic 43-kDa Fas, enhanced membrane levels of 43-kDa Fas, and induced Fas sensitivity. PC-3 cells expressed high levels of membrane 43-kDa Fas that were enhanced by VES treatments. Fas ligand expression by LNCaP cells was enhanced by VES treatments. In summary, VES triggers apoptosis in human prostate carcinoma cells but not normal prostate cells in vitro, and VES modulates Fas signaling

Methylation of the estrogen receptor CpG island in lung tumors is related to the specific type of carcinogen exposure.

Issa JP, Baylin SB, Belinsky SA.

*Cancer Res*. 1996 Aug 15; 56(16):3655-8.

Promoter methylation has recently been shown to be an alternative to mutation in inactivating tumor suppressor genes in human neoplasia. Although specific carcinogen exposures have been associated with characteristic mutation patterns in genes, the factors that lead to promoter hypermethylation remain unknown. One gene target for inactivation through promoter methylation is the estrogen receptor (ER). The purpose of this investigation was to determine the methylation status of this gene in lung tumors from smokers and those who never smoked and in rodents exposed to specific environmental carcinogens. Promoter methylation at the ER locus was detected in 4 of 11 tumors from never-smokers (36.4%) and 7 of 35 tumors from smokers (20%,  $P < 0.001$ ). Lung tumors induced by the tobacco-derived carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone also had a low incidence (16.7%) of ER methylation. In marked contrast, spontaneous and plutonium-induced tumors had a very high (81.8%) incidence of ER methylation. X-ray-induced tumors had an intermediate frequency of ER methylation (38.1%). The presence of ER methylation was associated with absent ER expression in rodent lung cancer cell lines. These results show for the first time that gene-specific promoter methylation can be modulated differentially depending on carcinogen exposure

Treatment with antioxidant and other nutrients in combination with chemotherapy and irradiation in patients with small-cell lung cancer.

Jaakkola K, Lahteenmaki P, Laakso J, et al.

*Anticancer Res*. 1992 May; 12(3):599-606.

Eighteen non-randomized patients with small cell lung cancer (4 women and 14 men, mean age 60.4, SD 7.8 years) received in addition to conservation small cell lung cancer treatment antioxidant treatment with vitamins, trace elements and fatty acids. All patients were out-patients who, except for one were also treated with chemotherapy and/or irradiation at regular intervals at a university of central hospital. Five patients (28%) were in an advanced stage of the disease. At the end of the follow-up period (31.7.90) the median survival time for the whole group was 505 days. Fourteen (77%) of the patients survived for more than 12 months and six patients (33%) for more than two years. One patient (5%) survived more than five years. Eight patients (44%) were still alive with a mean survival time of 32 months at the end of the study. Ten patients succumbed earlier from progression of the disease. Antioxidant treatment, in combination with chemotherapy and irradiation, prolonged the survival time of patients with small cell lung cancer compared to most published combination treatment regimens alone. We also noticed that the patients receiving antioxidants were able to tolerate chemotherapy and radiation treatment well. Surviving patients started antioxidant treatment in general earlier than those who succumbed

A cross-sectional study of vitamin intake in postoperative non-small cell lung cancer patients.

Jatoi A, Daly BD, Kramer G, et al.

*J Surg Oncol*. 1998 Aug; 68(4):231-6.

**BACKGROUND AND OBJECTIVES:** This cross-sectional study of postoperative non-small cell lung cancer (NSCLC) patients examined possible effects of vitamin intake and folate status on disease-free survival. **METHODS:** Supplemental vitamin usage, dietary vitamin intake (Willett Food Frequency Questionnaire), red blood cell (RBC) folate, and serum folate concentrations were assessed in patients with a history of NSCLC. Exclusion criteria included factors that alter folate status or that are associated with altered nutritional habits: (1) evidence of cancer on history, physical, or chest radiograph; (2) tobacco, alcohol ingestion (>2 drinks/ day), or cancer treatment within 3 months; (3) use of folate antagonists; and (4) age <60 years. **RESULTS:** 36 subjects were evaluated. The median disease-free censored survival was 24 months (range 4-41). Nineteen of 36 patients (53%) reported vitamin supplementation. Vitamin users had a longer median censored survival compared with nonusers (41 months versus 11 months;  $P = 0.002$ .) With adjustment for cancer stage, the association between RBC folate and censored survival ( $r = 0.35$ ;"  $P = 0.055$ ) and between serum folate and censored survival ( $r = 0.32$ ;"  $P = 0.083$ ) approached statistical significance. **CONCLUSIONS:** NSCLC patients who took vitamin supplements were more likely to be long-term survivors in the patients studied; a similar trend toward long-term survival was seen among patients with higher circulating folate concentrations

Vitamin E (d-alpha-tocopheryl succinate) decreases mitotic accumulation in gamma-irradiated human tumor, but not in normal, cells.

Jha MN, Bedford JS, Cole WC, et al.

*Nutr Cancer.* 1999; 35(2):189-94.

Previous studies have shown that treatment of tumor cells in vitro with d-alpha-tocopheryl succinate (alpha-TS), a most effective form of vitamin E, alone or in combination with X-irradiation, reduced the growth of these cells more than that produced by individual agents. However, it is unknown whether alpha-TS, alone or in combination with gamma-irradiation, would produce similar effects on normal cells. To study this, we have compared the effects of alpha-TS on three human tumor cell lines, HeLa (cervical carcinoma), OVGI (ovarian carcinoma), and A549 (lung carcinoma), with the effects on three human normal fibroblast lines, GM2149, AG1522, and HF19. Results showed that alpha-TS treatment of HeLa cells for 20 hours caused inhibition of growth in a dose-dependent manner, but normal human fibroblasts treated similarly with alpha-TS did not show such an effect. alpha-TS treatment for 20 hours also decreased mitotic accumulation in all three tumor cell lines but did not produce such an effect in any of the normal fibroblasts. As expected, gamma-irradiation with 1 Gy decreased mitotic accumulation in human tumor cells and normal fibroblasts; however, alpha-TS treatment for 24 hours before, during, and after irradiation for the entire experimental period further decreased mitotic accumulation in human tumor cells but not in normal cells. These data suggest that effects of alpha-TS, alone or in combination with gamma-irradiation, are selective for tumor cells. Therefore, existing fear that antioxidants such as vitamin E may protect cancer cells from free radical damage during radiation therapy is not justified

[Influence of methylcobalamin and cyanocobalamin on the neoplastic process in rats].

Kal'nev VR, Rachkus I, Kanopkaite SI.

*Prikl Biokhim Mikrobiol.* 1977 Sep; 13(5):677-81.

The effect of methylcobalamine (5,6-dimethylbenzimidazolyl-Co-methylcobamide, CH3-B12) and cyanocobalamine (5,6-dimethylbenzimidazolyl-Co-cyanocobamide, CN-B12) on the growth of Walker's carcinosarcoma and longevity of white noninbred rats with implanted Zajdela ascites hepatoma was studied. The two agents exerted a similar effect. They 1) reduced the survival of rats with implanted Zajdela ascites hepatoma and Walker's carcinosarcoma; 2) did not increase the cell concentration in ascites; and 3) increased the total volume of ascites

p16(INK4a) and histology-specific methylation of CpG islands by exposure to tobacco smoke in non-small cell lung cancer.

Kim DH, Nelson HH, Wiencke JK, et al.

*Cancer Res.* 2001 Apr 15; 61(8):3419-24.

The p16(INK4a) protein inhibits cyclin-dependent kinase 4, a key regulator of progression through the G(1) phase of the cell cycle. Methylation of CpG islands in the promoter region is an important avenue for inactivation of p16. The mechanism of methylation of the p16 promoter region, however, has not been elucidated. Recent reports investigating p16 methylation in non-small cell lung cancer (NSCLC) suggest that carcinogens in tobacco smoke induce the DNA methylation process. We investigated the association between methylation of the p16 promoter region and exposure to tobacco smoke in 185 primary NSCLCS: We also studied the relationship of p16 methylation with mutation of the K-ras and p53 genes, as well as with methylation at the DAP-kinase and p14(ARF) loci. Finally, we evaluated the prognostic significance of p16 methylation in NSCLC. The prevalence of p16 methylation was greater in squamous cell carcinoma (41%) compared with adenocarcinoma (22%;  $P = 0.03$ ; Fisher's exact test). Methylation of p16 was significantly associated with pack-years smoked ( $P = 0.007$ ;

Wilcoxon rank sum test), duration of smoking ( $P = 0.0009$ ; Wilcoxon rank sum test), and negatively with the time since quitting smoking ( $P = 0.03$ ; Wilcoxon rank sum test). No methylation of the nearby p14(ARF) locus was detected, and methylation of the DAP-kinase locus was not associated with either p16 methylation or with exposure to tobacco smoke. In patients with stage 1 adenocarcinoma, p16 methylation was an independent risk factor predicting significantly shorter postsurgery survival ( $P = 0.03$ ), controlling for the significant effects of other factors, including K-ras mutation. These findings suggest that methylation of CpG islands in tobacco-associated cancers occurs in a gene- and tissue-specific manner and is induced directly or indirectly by exposure to tobacco smoke in NSCLC

[Therapy of anthracycline-resistant metastatic breast carcinoma].

Kreienberg R.

*Schweiz Rundsch Med Prax.* 1998 Apr 22; 87(17):573-7.

Treatment of anthracycline-resistant metastatic breast cancer with new antineoplastic agents remains a challenge for the next future. The 5-year survival for this disease is only 15%, and hormonal and chemotherapeutic options remain essentially palliative. New treatment drugs or drug combinations are urgently needed to improve the prospects for patients with metastatic breast cancer, particularly for those with disease characteristics indicating a particularly poor prognosis. Taxanes are promising new drugs and have shown encouraging activity in patients with disease resistant to anthracyclines and in patients with visceral metastases, both with a poor prognosis. Paclitaxel (taxol) is applied with a dose of 175 mg/m<sup>2</sup> in a 3 hour infusion and docetaxel (taxotere) with a dose of 100 mg/m<sup>2</sup> q 3 weeks. Remission rates are expected between 6-30% for taxol and between 29-48% for docetaxel. Highly active in patients with anthracycline-resistant disease appears to be the vinca-alkaloid vinorelbine too. In patients treated with adriamycin objective remissions between 15-33% can be obtained. The long time known 5-fluorouracil comes to the third place of the effective drugs. Continuous infusion or addition of folic acid increases the intracellular efficacy and results in 5-53% objective remissions. In second-line chemotherapy platin-analogues together with etoposide, vincristine and 5-FU achieve partial or complete remissions between 19-37% for cisplatin containing and 5-12 for carboplatin containing combinations. This may eventually play a role especially if three drug combinations containing paclitaxel, epirubicin and vinorelbine will be used, which are reported to result in 20-33% complete response rates and 66% objective response. The indication for other new drugs like tomudex, topoisomerase-I-inhibitor and gemcitabine for anthracycline-resistant breast cancer remains to be established in multicenter studies

Homocysteine: an aetiological contributor to peripheral vascular arterial disease.

Kuan YM, Dear E, Grigg MJ.

*ANZ J Surg.* 2002 Sep; 72(9):668-71.

Surgeons are increasingly being exposed to the term 'hyperhomocysteinaemia' but few understand this condition that affects up to 10% of the population, or its pathological sequelae. Hyperhomocysteinaemia has been identified as an important and independent risk factor for atherosclerosis. There is increasing evidence that, in addition to coronary disease, hyperhomocysteinaemia is also associated with an increased risk of developing peripheral arterial disease. Causes of elevated homocysteine levels include inherited enzyme deficiencies and acquired vitamin deficiencies. Detection of hyperhomocysteinaemia is particularly relevant in patients with early onset atherosclerosis. Effective lowering of elevated homocysteine levels is possible with folate, vitamin B6 and B12 supplementation and may reduce the incidence and sequelae of atherosclerotic peripheral arterial disease

D-alpha-tocopheryl succinate (vitamin E) enhances radiation-induced chromosomal damage levels in human cancer cells, but reduces it in normal cells.

Kumar B, Jha MN, Cole WC, et al.

*J Am Coll Nutr.* 2002 Aug; 21(4):339-43.

**OBJECTIVE:** The purpose of this study was to measure and compare the effect of d-alpha-tocopheryl succinate (alpha-TS) in modifying radiation-induced chromosomal damage in human normal cells and cancer cells in culture. **METHODS:** Three human normal fibroblast cell lines (GM2149, AG1522 and HF19) and three human cancer cell lines, cervical cancer (HeLa) and ovarian carcinoma cells (OVGI and SKOV3) were treated with alpha-TS (37.6 microM) 20 hours before 100 cGy gamma-irradiation. After 30 minutes of irradiation, colcemid was added and cells were fixed. One hundred randomly selected metaphase cells were scored for the presence of chromatid gaps and breaks. To study the cellular accumulation of alpha-TS, cells were incubated in the presence of alpha-TS (18.8 and 37.6 microM) for 24 hours, and alpha-TS was extracted with hexane using a-tocopheryl acetate as an internal standard. The levels of alpha-TS were determined by HPLC. **RESULTS:** Results showed that alpha-TS induced chromosomal damage in both human cervical cancer cells and ovarian cancer cells, but not in human normal fibroblasts

in culture. In addition, alpha-TS enhanced the level of radiation-induced chromosomal damage in cancer cells, but it protected normal cells against such damage. Both cancer cells and normal cells accumulated similar levels of alpha-TS, suggesting that increased sensitivity of cancer cells to alpha-TS is acquired during transformation. CONCLUSION: The use of alpha-TS during radiation therapy may improve the efficacy of radiation therapy by enhancing tumor response and decreasing some of the toxicities on normal cells

Contribution of the antioxidative property of astaxanthin to its protective effect on the promotion of cancer metastasis in mice treated with restraint stress.

Kurihara H, Koda H, Asami S, et al.

*Life Sci.* 2002 Apr 21; 70(21):2509-20.

We investigated the effects of astaxanthin on the antitumor effector activity of natural killer (NK) cells suppressed by stress in mice in order to define the immunological significance of astaxanthin (ASX) when combined with restraint stress treatment. When the mice were treated with restraint stress alone, the total number of spleen cells, and the level NK cell activity per spleen were reduced to a nadir on day 3. The stress also caused a significant increase in the lipid peroxidation of liver tissue. ASX (100 mg/kg/day, p.o., 4 days) improved the immunological dysfunction induced by restraint stress. On the other hand, metastatic nodules were observed in the livers of syngenic DBA/2 mice on day 12 after inoculation of P815 mastocytoma cells. Hepatic metastasis was promoted further by restraint stress when applied on day 3 before the inoculation of P815. Daily oral administration of ASX (1 mg/kg/day, p.o., 14 days) markedly attenuated the promotion of hepatic metastasis induced by restraint stress. These results suggested that astaxanthin improves antitumor immune responses by inhibiting of lipid peroxidation induced by stress

Possible interactions between dietary antioxidants and chemotherapy.

Labriola D, Livingston R.

*Oncology (Huntingt).* 1999 Jul; 13(7):1003-8.

Many patients treat themselves with oral antioxidants and other alternative therapies during chemotherapy, frequently without advising their conventional health care provider. No definitive studies have demonstrated the long-term effects of combining chemotherapeutic agents and oral antioxidants in humans. However, there is sufficient understanding of the mechanisms of action of both chemotherapeutic agents and antioxidants to predict the obvious interactions and to suggest where caution should be exercised with respect to both clinical decisions and study interpretation. This article will describe these potential interactions and areas of concern, based on the available data. It will also suggest several potential courses of action that clinicians may take when patients indicate that they are taking or plan to use alternative therapies

Megadose vitamins in bladder cancer: a double-blind clinical trial.

Lamm DL, Riggs DR, Shriver JS, et al.

*J Urol.* 1994 Jan; 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

Antioxidants in cancer therapy; their actions and interactions with oncologic therapies.

Lamson DW, Brignall MS.

There is a concern that antioxidants might reduce oxidizing free radicals created by radiotherapy and some forms of chemotherapy, and thereby decrease the effectiveness of the therapy. The question has arisen whether concurrent administration of oral antioxidants is contraindicated during cancer therapeutics. Evidence reviewed here demonstrates exogenous antioxidants alone produce beneficial effects in various cancers, and except for a few specific cases, animal and human studies demonstrate no reduction of efficacy of chemotherapy or radiation when given with antioxidants. In fact, considerable data exists showing increased effectiveness of many cancer therapeutic agents, as well as a decrease in adverse effects, when given concurrently with antioxidants

Antioxidants and cancer therapy II: quick reference guide.

Lamson DW, Brignall MS.

*Altern Med Rev.* 2000 Apr; 5(2):152-63.

The previous lengthy review concerning the effects of antioxidant compounds used concurrently with radiotherapy and chemotherapy has been reduced to a reference guide. There are only three presently known examples in which any agent classifiable as an antioxidant has been shown to decrease effectiveness of radiation or chemotherapy in vivo. The vast majority of both in vivo and in vitro studies have shown enhanced effectiveness of standard cancer therapies or a neutral effect on drug action

Uterine restoration by radiation sequelae regression with combined pentoxifylline-tocopherol: a phase II study.

Letur-Konirsch H, Guis F, Delanian S.

*Fertil Steril.* 2002 Jun; 77(6):1219-26.

**OBJECTIVE:** To determine whether combined pentoxifylline (PTX) and tocopherol (vitamin E) treatment can improve uterine radiation-induced sequelae, resulting in an improved embryo implantation rate. **DESIGN:** Retrospective phase II clinical trial. **SETTING:** Volunteers in an oocyte donation program in a public hospital. **PATIENT(S):** Six women aged 31 +/- 4 years, who were irradiated 25 years previously for childhood cancer with 20 to 40 Gy including the pelvic area. **INTERVENTION(S):** Four women had taken hormone replacement therapy for primary amenorrhea, and two had retained their natural cycle. Treatment consisted of at least 12 months of pentoxifylline at 800 mg/day combined with 1000 IU/day of tocopherol. **MAIN OUTCOME MEASURE(S):** Endometrial thickness, uterine volume, and uterine artery blood flow were assessed by ultrasonography before and after pentoxifylline-tocopherol treatment, under usual estrogen-progesterone (OP) administration. **RESULT(S):** This treatment was well tolerated. All six patients improved significantly in endometrial thickness (6.2 +/- 0.6 vs. 3.2 +/- 1.1 mm), myometrial dimensions (44 [+/- 5] x 30 [+/- 3] x 20 [+/- 2] vs. 30 [+/- 7] x 22 [+/- 3] x 16 [+/- 2] mm), and diastolic uterine artery flow. **CONCLUSION(S):** In young women who want to bear children, the combination of pentoxifylline and vitamin E can reduce fibroatrophic uterine lesions after childhood irradiation

13-cis-retinoic acid plus interferon-alpha 2a in locally advanced squamous cell carcinoma of the cervix.

Lippman SM, Kavanagh JJ, Paredes-Espinoza M, et al.

*J Natl Cancer Inst.* 1993 Mar 17; 85(6):499-500.

13-cis-Retinoic acid plus interferon -2a: highly active systemic therapy for squamous cell carcinoma of the cervix.

Lippman SMPDRILM.

*J Natl Cancer Inst.* 1995;(84):241-5.

Low whole-blood S-adenosylmethionine and correlation between 5-methyltetrahydrofolate and homocysteine in coronary artery disease.

Loehrer FM, Angst CP, Haefeli WE, et al.

*Arterioscler Thromb Vasc Biol.* 1996 Jun; 16(6):727-33.

Mild elevation of plasma homocysteine is an independent risk factor for vascular disease. We studied the role of 5-methyltetrahydrofolate (5-MTHF), the folate form directly involved in homocysteine metabolism, in contrast to previous studies, which used total folate measurements, in 70 coronary artery disease (CAD) patients and control subjects. We also measured S-adenosylmethionine (SAM), which controls the activity of critical enzymes of homocysteine metabolism. Fasting plasma total homocysteine was elevated ( $> 12.4$   $\mu\text{mol/L}$  for women,  $> 13.3$   $\mu\text{mol/L}$  for men) in 17% of patients, in accordance with earlier studies. These patients showed lower 5-MTHF ( $12.4 \pm 1.0$   $\mu\text{mol/L}$ , mean  $\pm$  SD) than control subjects ( $24.2 \pm 15.0$ ,  $P < .001$ ), and there was a clear correlation (multiple linear regression analysis:  $P = .002$ ) of this relevant form of folate with homocysteine. However, 37% of the normohomocysteinemic patients also revealed similarly low 5-MTHF levels, suggesting that a decrease of 5-MTHF does not necessarily cause hyperhomocysteinemia. SAM was significantly decreased in patients ( $1.4 \pm 0.4$   $\mu\text{mol/L}$ ) compared with control subjects ( $1.8 \pm 0.3$ ,  $P < .001$ ) but was not correlated to homocysteine or 5-MTHF. The correlation between homocysteine and 5-MTHF that was found in CAD patients but not in control subjects confirms the direct relationship between these compounds in vivo. The new finding of low SAM in patients demands further studies, since it might indicate that low levels pose risk and that SAM might be a protective factor against the development of CAD

[Fluorouracil as monotherapy or combined with folinic acid in the treatment of metastasizing colorectal carcinoma].

Loffler TM, Korsten FW, Reis HE, et al.

*Dtsch Med Wochenschr.* 1992 Jun 26; 117(26):1007-13.

In a prospective randomized multicentre trial 139 patients with metastatic colorectal carcinoma (70 men, 69 women; age 35-81 years) were given palliative treatment with fluorouracil (400 mg/m<sup>2</sup> daily for 5 days) alone or combined with folic acid (100 mg/m<sup>2</sup> before each dose of fluorouracil). Both groups were comparable in respect of age, sex, Karnofsky index and number of localisations of metastases. The criterion for starting the treatment was progression of the malignancy or clinical symptoms caused by the tumour. Resulting remission rates (fluorouracil monotherapy vs combination with folic acid) were: complete or partial remission, 9 vs 16%; arrest of tumour growth, 20 vs 60%; progression 71 vs 24%. Peripheral side effects, such as stomatitis and diarrhoea, were similarly frequent with the two treatment regimens and reasonably tolerable. Median survival time for the fluorouracil monotherapy was 7.24 months from onset of treatment, and 9.1 months from the time that any metastases were diagnosed. The combination treatment with folic acid achieved a significantly longer median survival time ( $P$  less than 0.0001), 14.98 months from treatment onset and 16.3 months from metastasis diagnosis. The higher rate of response and the significantly prolonged survival time signify an improvement of the therapeutic profile of fluorouracil by addition of folic acid in the palliative therapy of colorectal carcinomas

Vitamin E inhibits protein kinase C activity.

Mahoney CW, Azzi A.

*Biochem Biophys Res Commun.* 1988 Jul 29; 154(2):694-7.

Vitamin E (dl-alpha-tocopherol) has been found to inhibit in vitro brain protein kinase c with a half inhibitory concentration of 450 microM. The known plasma concentrations of vitamin E are one order of magnitude lower than the protein kinase c half-inhibitory concentration but it is also known that, at the membrane level where the active protein kinase c is located, the lipophilic vitamin E is more concentrated (Burton, G.W., Joyce, A. and Ingold, K.U. and Locke, S. (1983) Arch. Biochem. Biophys. 221, 281-290). It appears that vitamin E, in addition to its antioxidant function, may play a role in regulating the activity of protein kinase c

Vitamin E succinate promotes breast cancer dormancy and inhibits VEGF gene expression. Paper presented at the International Congress on Frontiers of Pharmacology and Therapeutics in the 21st Century, New Delhi, India, December 1999, pp. 15-9.

Malafa MPNLT.

1999;December 1999,15-9.

A short-term dietary supplementation of high doses of vitamin E increases T helper 1 cytokine production in patients with advanced colorectal cancer.

Malmberg KJ, Lenkei R, Petersson M, et al.

*Clin Cancer Res.* 2002 Jun; 8(6):1772-8.

PURPOSE: Patients with advanced cancer exhibit multifaceted defects in their immune capacity, which are likely to contribute

to an increased susceptibility to infections and disease progression and to constitute a barrier to immunotherapeutic interventions. A chronic inflammatory condition associated with increased oxidative stress has been suggested as one of the responsible mechanisms behind the tumor-induced immune suppression. We, therefore, speculated that supplementation with the antioxidant vitamin E could enhance the immune functions in patients with advanced cancer. EXPERIMENTAL DESIGN: This hypothesis was here tested in twelve patients with colorectal cancer (Dukes' C and D) who, prior to intervention with chemo- or radiotherapy, received a daily dose of 750 mg of vitamin E during a period of 2 weeks. RESULTS: Short-term supplementation with high doses of dietary vitamin E leads to increased CD4:CD8 ratios and to enhanced capacity by their T cells to produce the T helper 1 cytokines interleukin 2 and IFN-gamma. In 10 of 12 patients, an increase of 10% or more (average, 22%) in the number of T cells producing interleukin 2 was seen after 2 weeks of vitamin E supplementation, as compared with peripheral blood monocyte samples taken before treatment (P = 0.02). Interestingly, there seemed to be a more pronounced stimulatory effect by vitamin E on naive (CD45RA(+)) T helper cells as compared with T cells with a memory/activated phenotype. CONCLUSIONS: Dietary vitamin E may be used to improve the immune functions in patients with advanced cancer, as a supplement to more specific immune interventions

Protection of normal tissues from the cytotoxic effects of radiation therapy: focus on amifostine.

Mehta MP.

*Semin Radiat Oncol.* 1998 Oct; 8(4 Suppl 1):14-6.

Evidence for the use of amifostine (Ethyol, ALZA Pharmaceuticals, Palo Alto, CA/US Bioscience, West Conshohocken, PA) as a radioprotectant has been gathered in a number of clinical trials conducted over the past decade. This report briefly reviews those trials, as well as highlights results of a recent phase II trial conducted to evaluate the efficacy of daily amifostine administration in reducing the incidence of radiation-induced esophagitis in patients with stage III non-small cell lung cancer. Of 25 patients evaluated, none experienced grade 3 or 4 esophagitis or dyspnea. No patients required discontinuation of therapy due to amifostine-induced hypotension. There was a 60% objective response rate and 1-, 2-, and 3-year survival rates were 55%, 23%, and 23%, respectively. Thus, amifostine administration reduced radiation-induced toxicities without reducing antitumor efficacy

Role of vitamin A and its derivatives in the treatment of human cancer. In *Nutrients in Cancer Prevention and Treatment* 1995.

Meyskens FL, Jr.

2004;349-62.

The modifying effect of beta-carotene on radiation and chemotherapy induced oral mucositis.

Mills EE.

*Br J Cancer.* 1988 Apr; 57(4):416-7.

Potential of 5-aza-2'-deoxycytidine (Decitabine) a potent inhibitor of DNA methylation for therapy of advanced non-small cell lung cancer.

Momparler RL, Ayoub J.

*Lung Cancer.* 2001 Dec; 34 Suppl 4:S111-S115.

Although new agents and drug combinations have increased the response rate in advanced non-small cell lung cancer (NSCLC), long-term survivors are rare. There is an urgent need to develop new chemotherapeutic approaches for disease. In a previous pilot phase I-II study on 5-aza-2'-deoxycytidine (5-AZA-CdR) in patients with stage IV NSCLC, we observed several interesting responses, including one patient that was still alive (68 months) at the time of publication of our results. In the present report, we want to point out the long-term follow up of this patient, who survived 81 months, and discuss the interesting mechanism of action of 5-AZA-CdR that may have been responsible for this interesting response. 5-AZA-CdR is a potent inhibitor of DNA methylation. Recent progress in this field has shown that aberrant methylation of the promoter region of tumor suppressor genes inhibits their expression. This epigenetic event can contribute to tumorigenesis. Since 5-AZA-CdR can reactivate these genes by blocking DNA methylation, it has the potential to reverse tumorigenesis. This novel mode of action makes it an interesting agent to investigate for the chemotherapy of malignant disease, including lung cancer

Does vitamin E prevent breast cancer?

Morrow M.

*Life Extension Magazine* 2002 May. 2002; 2002 May 8(5):29-32.

Questioning Chemotherapy.

Moss RW.

1995;

Methotrexate and folic acid effect in normal and sarcoma 180 bearing mice.

Motycka K, Balcarova A.

*Neoplasma*. 1975; 22(5):507-18.

Four- to six-fold surplus of folic acid in oral application reduced the toxicity of methotrexate administered repeatedly in high therapeutic doses. The therapeutic effect of methotrexate applied intraperitoneally to mice with the ascitic S 180 sarcoma, as measured by their survival, can be reliably demonstrated; moreover, the survival can be prolonged by adding folic acid into drinking water. In the solid form S 180 the intraperitoneal administration of methotrexate did not significantly reduce the weight of tumors of treated animals as compared to untreated animals. The maximum tolerated dose of methotrexate was lower in animals with the ascitic tumor than in non-tumorous animals

Vitamin C in leukemia and preleukemia cell growth.

Park CH.

*Prog Clin Biol Res*. 1988; 259:321-30.

Vitamin C was shown to be an essential requirement for the growth of mouse myeloma cells in an in vitro colony assay. Human leukemia (acute nonlymphocytic leukemia) cell colonies grow well in a similar in vitro culture system, and vitamin C has been shown to enhance the growth of leukemic cell colonies in 77 (35%) of 219 leukemic patients while none of 34 normal bone marrows tested simultaneously shows growth enhancement by this vitamin. This vitamin C effect is reproducible in repeated experiments in same patients, specific to this vitamin, selective for leukemic cells, and is proven to be biological in nature. Further, leukemic cells are mobilized back and forth between cycling and resting states with vitamin C supplementation/depletion. Our more recent study indicates that the preleukemia (myelodysplastic syndrome), generally known to be related to acute nonlymphocytic leukemia, has similar pattern in terms of vitamin C sensitivity, with 8 of 25 patients (32%) showing the growth enhancement with this vitamin

Potential of the effect of paclitaxel and carboplatin by antioxidant mixture on human lung cancer H520 cells.

Pathak AK, Singh N, Khanna N, et al.

*J Am Coll Nutr*. 2002 Oct; 21(5):416-21.

**OBJECTIVE:** Antioxidants have been shown to enhance the effect of certain chemotherapeutic agents on tumor cells in culture. However, this effect differs depending upon the type of tumor and the drugs. In this study, the objective was to see whether pretreatment with antioxidant mixture could enhance the cytotoxic and apoptotic effect of commonly used chemotherapeutic agents, paclitaxel and carboplatin for the treatment of NSCLC. **METHODS:** Human lung squamous cell carcinoma cell line, H520, was treated with antioxidant mixture (vitamin C, vitamin E and beta carotene), paclitaxel and carboplatin, individually and in combination of different doses in different sequences. Growth inhibition and induction of apoptosis was studied by morphological changes, MTT assay and flow-cytometric analysis. **RESULTS:** The antioxidant mixture by itself led to 15% apoptosis in H520 cells. Paclitaxel treatment 24 hours prior to carboplatin caused 54% apoptosis, more than that produced by simultaneous treatment with both agents (40%). A statistically significant improvement in the degree of apoptosis, induced by paclitaxel and carboplatin combination, was seen when the cells were pretreated with antioxidant mixture immediately before paclitaxel exposure (70%) or 24 hours before paclitaxel exposure (89%). **CONCLUSION:** The data suggests that the apoptotic effects of paclitaxel and carboplatin are enhanced by pretreatment with the antioxidant mixture. Thus, the most promising sequence of these agents, which emerged in this study, was pretreatment with antioxidant mixture for 24 hours followed by paclitaxel treatment for 24 hours followed by carboplatin exposure for 24 hours

A preliminary clinical trial in patients with non-small cell lung carcinoma (carboplatin and Taxol together with high doses of

vitamin C, vitamin E, and beta-carotene vs. carboplatin and Taxol alone) (unpublished data).

Pathak S.

7777;unpublished data

Effect of combined ascorbic acid and B-12 on survival of mice with implanted Ehrlich carcinoma and L1210 leukemia.

Poydock ME.

*Am J Clin Nutr.* 1991 Dec; 54(6 Suppl):1261S-5S.

A combination of dehydroascorbic acid and hydroxycobalamin (vitamin B-12) inhibited mitoses of tumors in mice. The present study was performed to test the effect of these vitamins on the survival of mice bearing carcinomas and leukemias. In each assay 40 mice received 0.1 mL ip tumor cells ( $\times 10^5$ ). After 24 h, 20 mice were injected with 0.2 mL (0.4 g/kg body wt) of the vitamins daily for 10 d. All controls died by day 19, but greater than 50% of the treated mice were alive after 60 d. In vitro findings revealed inhibition of mitoses in L1210 leukemia cells, but not in normal L929 cells. In recent research with cobalt-ascorbate plus vitamin C, we demonstrated that when B-12 is combined with vitamin C, the cobalt nucleus of B-12 attaches to a carbon on vitamin C, forming cobalt ascorbate. Tests proved that cobalt ascorbate plus vitamin C also inhibited tumor cells

Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture.

Prasad KN, Sinha PK, Ramanujam M, et al.

*Proc Natl Acad Sci U S A.* 1979 Feb; 76(2):829-32.

Mouse neuroblastoma (NB) cells in culture were more sensitive to sodium L-ascorbate than were rat glioma cells by the criterion of growth inhibition (due to cell death and reduction in cell division). Sodium L-ascorbate at nonlethal concentrations potentiated the effect of 5-fluorouracil (FUra), x-irradiation, bleomycin, RO20-1724, prostaglandin E1, and sodium butyrate on NB cells but did not produce such an effect on glioma cells. Sodium L-ascorbate did not enhance the effect of vincristine, 6-thioguanine, or 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) except at higher drug doses and it reduced the cytotoxic effect of methotrexate and 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) on NB cells. Sodium D-ascorbate produced effects similar to those produced by sodium L-ascorbate on NB cells. L-Ascorbic acid-2-sulfate (barium salt) affected neither the growth rate nor the effect of 5-FUra on NB cells. Glutathione, a reducing agent, was more toxic to NB cells in comparison to D- OR L-ascorbate; however, at a similar concentration it failed to potentiate the effect of 5-FUra on NB cells

Effects of tocopherol (vitamin E) acid succinate on morphological alterations and growth inhibition in melanoma cells in culture.

Prasad KN, Edwards-Prasad J.

*Cancer Res.* 1982 Feb; 42(2):550-5.

The effects of various forms of tocopherol (vitamin E) on the growth and differentiation of mouse melanoma (B-16) and mouse fibroblast (L-cells) cells in culture were studied. D-alpha-tocopherol acid succinate induced morphological alterations and growth inhibition in melanoma cells. When vitamin E acid succinate was removed 4 days after treatment, the above changes remained irreversible for a period of 24 hr, after which resistant cells and partially affected cells renewed cell division and eventually reached confluency. The relative efficacy of D and DL forms of vitamin E acid succinate remains to be evaluated. However, other forms of vitamin E such as DL-alpha-tocopherol free alcohol, Aquasol DL-alpha-tocopherol acetate, DL-alpha-tocopherol nicotinate, or sodium succinate with an equivalent volume of ethanol, at similar concentrations, were ineffective. Vitamin E acid succinate at similar concentrations did not induce morphological changes in fibroblasts. Melanoma cells were about 2-fold more sensitive to vitamin E acid succinate than were fibroblasts for the criterion of growth inhibition. Vitamin E acid succinate-induced morphological changes and growth inhibition in melanoma cells were expressed in hormone-supplemented serum-free medium, but the concentration requirement was about 5 times less than that needed in serum-supplemented medium. Although cyclic adenosine 3': 5'-monophosphate-stimulating agents are known to cause growth inhibition and morphological changes in melanoma cells in culture, vitamin E acid succinate-induced morphological alterations in melanoma cells are not mediated by a rise in cellular cyclic adenosine 3':5'-monophosphate. Ethanol was sufficient to increase the melanin content in melanoma cells. These data show that vitamin E acid succinate may be a potentially useful tumor therapeutic agent

Expressions of some molecular cancer risk factors and their modification by vitamins.

Prasad KN, Edwards-Prasad J.

*J Am Coll Nutr.* 1990 Feb; 9(1):28-34.

Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins.

Prasad KN, Hernandez C, Edwards-Prasad J, et al.

*Nutr Cancer.* 1994; 22(3):233-45.

The effect of a mixture of vitamins in modifying the efficacy of commonly used drugs in the treatment of human melanoma has not been studied. Vitamin C and d-alpha-tocopheryl succinate (alpha-TS) alone reduced the growth of human melanoma (SK-30) cells in culture, whereas beta-carotene (BC), 13-cis-retinoic acid (RA), or sodium selenite alone was ineffective. RA caused morphological changes, as evidenced by flattening of cells and formation of short cytoplasmic processes. A mixture of four vitamins (vitamin C, BC, alpha-TS, and RA) was more effective in reducing growth of human melanoma cells than a mixture of three vitamins. The growth-inhibitory effect of cis-platin, decarbazine, tamoxifen, and recombinant interferon-alpha 2b was enhanced by vitamin C alone, a mixture of three vitamins (BC, alpha-TS, and RA), and a mixture of four vitamins (vitamin C, BC, alpha-TS, and RA) that contained 50 micrograms/ml of vitamin C. These data show that a mixture of three or four vitamins can enhance the growth-inhibitory effect of currently used chemotherapeutic agents on human melanoma cells

Effect of individual and multiple antioxidant vitamins on growth and morphology of human nontumorigenic and tumorigenic parotid acinar cells in culture.

Prasad KN, Kumar R.

*Nutr Cancer.* 1996; 26(1):11-9.

The effects of individual and multiple antioxidant vitamins on growth and morphology of human nontumorigenic (2HPC8) and tumorigenic (2HP1G) parotid acinar cells in culture have not been investigated. Our study showed that tumorigenic acinar cells were more sensitive than nontumorigenic acinar cells to individual vitamins such as vitamin C, beta-carotene (BC), d-alpha-tocopheryl succinate (alpha-TS), and retinoic acid (RA) and a mixture of four vitamins (vitamin C, BC, alpha-TS, and RA). The effect of individual vitamins on tumorigenic acinar cells depended on the dose and the type of vitamins. Vitamin C at a low concentration stimulated growth, but at a high concentration it inhibited growth. BC was most effective in reducing growth, and it alone caused extensive morphological changes in tumorigenic acinar cells. A mixture of four vitamins at appropriate doses was more effective than a mixture of two or three vitamins at the same doses in reducing the growth of tumorigenic acinar cells. The extent of growth inhibition depended on the dose and the type of vitamins. Our results suggest that the use of multiple antioxidant vitamins is essential for a maximal reduction in cancer incidence among a high-risk population. The use of one or two vitamins may be ineffective or even harmful

Cancer prevention studies: past, present, and future directions.

Prasad KN, Cole W, Hovland P.

*Nutrition.* 1998 Feb; 14(2):197-210.

In spite of extensive research on vitamins and diet, a consistent beneficial role of vitamin supplements, together with diet modification in human cancer prevention, has not been demonstrated. Published results of human intervention trials with vitamin supplements have been contradictory. This review critically, but briefly, evaluates (a) current concepts of human carcinogenesis, (b) effects of vitamins on biochemical parameters that are pertinent to cancer prevention, and (c) whether past or current protocols for intervention trials among high-risk populations adopt specific scientific rationales that are based on laboratory and human epidemiology studies. In addition, we propose a novel experimental design for intervention trials among high-risk human populations that is based on sound scientific principles derived from laboratory and human epidemiologic data on vitamins, diet, lifestyle, and cancer prevention. Such trials would answer a fundamental public health issue of today: Does supplementation with multiple vitamins, together with diet and lifestyle modifications, reduce the risk of cancer?

High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy.

Prasad KN, Kumar A, Kochupillai V, et al.

*J Am Coll Nutr.* 1999 Feb; 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

Scientific rationale for using high-dose multiple micronutrients as an adjunct to standard and experimental cancer therapies.

Prasad KN, Cole WC, Kumar B, et al.

*J Am Coll Nutr.* 2001 Oct; 20(5 Suppl):450S-63S.

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

Enhancement of apoptosis and inhibition of brain tumor growth in transgenic mice by depletion of antioxidants. American Society for Cell Biology Annual Meeting.

Salganik RACRJ.

*Am Soc Cell Biol.* 1999;

444a

Dietary antioxidant depletion: enhancement of tumor apoptosis and inhibition of brain tumor growth in transgenic mice.

Salganik RI, Albright CD, Rodgers J, et al.

*Carcinogenesis.* 2000 May; 21(5):909-14.

Apoptosis, or regulated cell suicide, eliminates unwanted and damaged cells, including precancerous and cancerous cells. Since reactive oxygen species (ROS) act as essential apoptotic mediators, we reasoned that increasing the ROS level might enhance apoptosis and thereby slow down tumor growth. Here, using a defined transgenic brain tumor model with known tumor apoptosis rates, we test the impact of antioxidant-depleted diet, capable of increasing ROS levels, or antioxidant-enriched diets on tumor growth. Dramatically increased apoptosis occurs within tumors, but not in normal tissues of antioxidant-depleted mice. The presence of detectable increased oxidant stress within tumors indicates that the likely mechanism of enhanced tumor apoptosis is via ROS and DNA oxidative impairment. Importantly, due to the ROS-enhanced apoptosis, tumor growth is inhibited in mice fed an antioxidant-depleted diet. In clear contrast, an antioxidant-rich diet had no impact on tumor growth

The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population.

Salganik RI.

*J Am Coll Nutr.* 2001 Oct; 20(5 Suppl):464S-72S.

Cellular oxidants, called reactive oxygen species (ROS), are constantly produced in animal and human cells. Excessive ROS can induce oxidative damage in cell constituents and promote a number of degenerative diseases and aging. Cellular antioxidants protect against the damaging effects of ROS. However, in moderate concentrations, ROS are necessary for a number of protective reactions. Thus, ROS are essential mediators of antimicrobial phagocytosis, detoxification reactions carried out by the cytochrome P-450 complex, and apoptosis which eliminates cancerous and other life-threatening cells. Excessive antioxidants could dangerously interfere with these protective functions, while temporary depletion of antioxidants can enhance anti-cancer effects of apoptosis. Experimental data are presented supporting these notions. The human population is heterogeneous regarding ROS levels. Intake of exogenous antioxidants (vitamins E, C, beta-carotene and others) could protect against cancer and other degenerative diseases in people with innate or acquired high levels of ROS. However, abundant antioxidants might suppress these protective functions, particularly in people with a low innate baseline level of ROS. Screening human populations for ROS levels could help identify groups with a high level of ROS that are at a risk of developing cancer and other degenerative diseases. It also could identify groups with a low level of ROS that are at a risk of down-regulating ROS-dependent anti-cancer and other protective reactions. Screening populations could provide a scientifically grounded application of antioxidant supplements, which could significantly contribute to the nation's health

Progesterone receptor B gene inactivation and CpG hypermethylation in human uterine endometrial cancer.

Sasaki M, Dharia A, Oh BR, et al.

*Cancer Res.* 2001 Jan 1; 61(1):97-102.

The expressions of two isoforms of human progesterone receptor (PR) are under the control of the two different promoters. Recent studies revealed differences between these isoforms, PRA and PRB, in their expression and function in endometrial cells. Aberrant methylation of normally unmethylated CpG islands has been associated with inactivation of several genes in human cancers. In this study, we investigated the methylation status and the expression of the two different PR isoforms, PRA and PRB, in uterine endometrial carcinoma (UEC) using methylation-specific PCR (MSP), reverse transcription-PCR (RT-PCR), the 5' rapid amplification of cDNA ends method (5'RACE), and immunohistochemical staining. The results of RT-PCR and 5'RACE suggest that only PRB is inactivated, although PRA is activated in all UEC cell lines. Treatment with a demethylating agent, 5-aza-2'-deoxycytidine, restored PRB expression in all cell lines, suggesting that inactivation of this gene is through methylation. By MSP and direct DNA sequencing, PRB was methylated, whereas PRA was unmethylated in all of the cell lines. To determine the methylation status of PRB in UEC patients, we investigated 83 cancerous and 33 normal samples. Sixty-two of 83 cancer samples had only methylated alleles of PRB, although all cancer samples had only unmethylated PRA alleles. Seventy-one of 83 cancer samples were negative for PRB expression. All 62 cancer samples that had only methylated PRB alleles were negative for PRB expression. No significant changes were observed in PRA methylation status or immunohistochemistry positivity in normal and cancer samples. To determine whether de novo methylation of PRB occurred in UEC patients, we studied 32 pairs of cancer and normal samples from the same patient. Twenty of 32 cancer samples had only methylated PRB alleles, although all 32 normal samples had only unmethylated PRB alleles. The loss of unmethylated alleles was well correlated with negativity in immunohistochemical staining for PRB. This is the first report of the selective methylation and the subsequent silencing of PRB in uterine endometrial cancer

Molecular and biochemical control of tumor growth following treatment with carotenoids or tocopherols. In *Nutrients in Cancer Prevention and Treatment*.

Schwartz JL.

1995;287-316.

Vitamin A and  $\beta$ -carotene as adjunctive therapy to tumor excision, radiation therapy and chemotherapy. In *Vitamins, Nutrition and Cancer* 1984, pp. 1-19.

Seifter ERAPJLSM.

1984;1-19.

Experimental study of antitumor effect of methyl-B12.

Shimizu N, Hamazoe R, Kanayama H, et al.

*Oncology.* 1987; 44(3):169-73.

We examined the antitumor effect of vitamin B12 (methyl-B12) using C3H/He, C57BL/6 and BALB/C mice for animals and MH134 hepatoma ascites cells, Lewis lung cancer cells and Ehrlich ascites tumor cells for tumor cells. At 1.0-10 micrograms/ml, methyl-B12 enhanced PHA- and Con-A-induced lymphocyte blastoformation of C3H/He mice. The growth of MH134 tumors on the backs of C3H/He mice were suppressed by the 7-day administration of 50 or 100 micrograms/day i.p. and their survival was longer than that of untreated mice. However, methyl-B12 administration did not positively affect the survival of C3H/He mice that had been irradiated with 60Co 300 R on the day before tumor cell inoculation. The growth of Ehrlich ascites tumor cells inoculated into BALB/C mice was also reduced at 17 and 19 days after tumor inoculation by administration of methyl-B12 50 micrograms/day i.p. and the mice survived longer than the untreated mice

Antioxidants with Radiation and Chemotherapy? 2000. *Comprehensive Cancer Care* 2001.

Simone C.

2000;2001;

Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer.

Somasundaram S, Edmund NA, Moore DT, et al.

*Cancer Res.* 2002 Jul 1; 62(13):3868-75.

Curcumin, the major component of the spice turmeric, is used as a coloring and flavoring additive in many foods and has attracted interest because of its anti-inflammatory and chemopreventive activities. However, this agent also inhibits the generation of reactive oxygen species (ROS) and the c-Jun NH(2)-terminal kinase (JNK) pathway, and because many chemotherapeutic drugs generate ROS and activate JNK in the course of inducing apoptosis, we considered the possibility that curcumin might antagonize their antitumor efficacy. Studies in tissue culture revealed that curcumin inhibited camptothecin-, mechlorethamine-, and doxorubicin-induced apoptosis of MCF-7, MDA-MB-231, and BT-474 human breast cancer cells by up to 70%. Inhibition of programmed cell death was time and concentration dependent, but occurred after relatively brief 3-h exposures, or at curcumin concentrations of 1 microM that have been documented in Phase I chemoprevention trials. Under these conditions, curcumin exhibited antioxidant properties and inhibited both JNK activation and mitochondrial release of cytochrome c in a concentration-dependent manner. Using an in vivo model of human breast cancer, dietary supplementation with curcumin was found to significantly inhibit cyclophosphamide-induced tumor regression. Such dietary supplementation was accompanied by a decrease in the activation of apoptosis by cyclophosphamide, as well as decreased JNK activation. These findings support the hypothesis that dietary curcumin can inhibit chemotherapy-induced apoptosis through inhibition of ROS generation and blockade of JNK function, and suggest that additional studies are needed to determine whether breast cancer patients undergoing chemotherapy should avoid curcumin supplementation, and possibly even limit their exposure to curcumin-containing foods

Role of retinoids in differentiation and carcinogenesis.

Sporn MB, Roberts AB.

*Cancer Res.* 1983 Jul; 43(7):3034-40.

Improvement of the recurrence-free interval using biological adjuvant therapy in uveal melanoma.

Tallberg T, Uusitalo R, Sarna S, et al.

*Anticancer Res.* 2000 May; 20(3B):1969-75.

This study was an attempt to compensate for an alleged aetiological deficiency in melanoma by the prophylactic oral administration of the essential biological components missing. Nine random patients suffering from high-risk uveal melanoma (T3) were, in this preliminary study, treated secondarily with biological dietary adjuvants after primary standard therapy, enucleation or brachytherapy. Secondary treatment consisted of certain natural amino-acids, trace-element salts, folic acid and a diet containing neurogenic lipid components. It entailed no side-effects, no toxicity and was inexpensive. None of these nine patients has suffered recurrent disease. The mean follow-up time was over 80 months (median 69, range 58-140 months). Local tumour control was 100%. This clinical result is significantly better ( $p = 0.018$ ) as compared to similar T3 uveal melanoma patients in standard care who did not receive adjuvant dietary remedies after primary treatment. The control patients consisted of similar adjusted T3 cases selected from the Swedish official registries, and T2 patients from Germany. Based on the previous positive clinical results obtained with cutaneous malignant melanoma in bioimmunotherapy this additional positive result supports the notion that biological components administered orally may compensate for the etiological deficiency leading to

malignant melanoma

Vitamin E succinate induction of HL-60 cell adhesion: a role for fibronectin and a 72-kDa fibronectin-binding molecule.

Turley JM, Sanders BG, Kline K.

*Nutr Cancer*. 1995; 23(1):43-54.

HL-60 cells, growing as single cells in suspension, exhibit marked cell-cell adhesion when treated for 24 hours with 10 micrograms/ml RRR-alpha-tocopheryl succinate, also called vitamin E succinate (VES). VES-induced cell-cell adhesion is dependent on divalent cations and a functional cytoskeleton and is protein mediated. Cell adhesion molecules CD11a/CD18, CD11b/CD18, CD29, and CD54 do not appear to be mediating VES-induced cell adhesion. HL-60 cells treated with VES adhere to fibronectin-coated plastic and secrete elevated levels of fibronectin. A 72-kDa fibronectin-binding membrane molecule was detected on VES-treated HL-60 cells, and antibodies to fibronectin were shown to inhibit VES-induced cell aggregation. VES induction of HL-60 cell-cell adhesion is proposed to result from increased amounts of extracellular fibronectin binding to VES-induced cell surface fibronectin-binding molecules

Frequent k- ras -2 mutations and p16(INK4A)methylation in hepatocellular carcinomas in workers exposed to vinyl chloride.

Weihrauch M, Benicke M, Lehnert G, et al.

*Br J Cancer*. 2001 Apr 6; 84(7):982-9.

Vinyl chloride (VC) is a known animal and human carcinogen associated with liver angiosarcomas (LAS) and hepatocellular carcinomas (HCC). In VC-associated LAS mutations of the K- ras -2 gene have been reported; however, no data about the prevalence of such mutations in VC associated HCCs are available. Recent data indicate K- ras -2 mutations induce P16 methylation accompanied by inactivation of the p16 gene. The presence of K- ras -2 mutations was analysed in tissue from 18 patients with VC associated HCCs. As a control group, 20 patients with hepatocellular carcinoma due to hepatitis B (n = 7), hepatitis C (n = 5) and alcoholic liver cirrhosis (n = 8) was used. The specific mutations were determined by direct sequencing of codon 12 and 13 of the K- ras -2 gene in carcinomatous and adjacent non-neoplastic liver tissue after microdissection. The status of p16 was evaluated by methylation-specific PCR (MSP), microsatellite analysis, DNA sequencing and immunohistochemical staining. All patients had a documented chronic quantitated exposure to VC (average 8883 ppm, average duration: 245 months). K- ras -2 mutations were found in 6 of 18 (33%) examined VC-associated HCCs and in 3 cases of adjacent non-neoplastic liver tissue. There were 3 G --> A point mutations in the tumour tissue. All 3 mutations found in non-neoplastic liver from VC-exposed patients were also G --> A point mutations (codon 12- and codon 13-aspartate mutations). Hypermethylation of the 5' CpG island of the p16 gene was found in 13 of 18 examined carcinomas (72%). Of 6 cancers with K- ras -2 mutations, 5 specimens also showed methylated p16. Within the control group, K- ras -2 mutations were found in 3 of 20 (15%) examined HCC. p16 methylation occurred in 11 out of 20 (55%) patients. K- ras -2 mutations and p16 methylation are frequent events in VC associated HCCs. We observed a K- ras -2 mutation pattern characteristic of chloroethylene oxide, a carcinogenic metabolite of VC. Our results strongly suggest that K- ras -2 mutations play an important role in the pathogenesis of VC-associated HCC

Homocystinuria due to cystathionine beta-synthase deficiency--the effects of betaine treatment in pyridoxine-responsive patients.

Wilcken DE, Dudman NP, Tyrrell PA.

*Metabolism*. 1985 Dec; 34(12):1115-21.

Homocystinuria due to cystathionine beta-synthase deficiency may be responsive to pyridoxine, a precursor of the cofactor pyridoxal phosphate, and the amount of residual enzyme activity present is the probable determinant of this. In six treated pyridoxine-responsive patients whose biochemical control of fasting plasma amino acid levels appeared optimal, we assessed the effects on plasma amino acids of standard oral methionine loads (4g/m<sup>2</sup> of body area) before and after adding betaine (trimethylglycine) 6 g/d, to the treatment regimen of pyridoxine and folic acid. Our aim was to define the capacity of these patients to metabolize methionine and to determine whether betaine would effect a reduction in postload homocysteine levels. During the 24 hours after the methionine challenge all patients had higher plasma methionine and homocysteine and lower cysteine than did 17 normal subjects. After betaine these homocysteine responses were reduced to near normal, and there was a trend toward increased methionine. There was a direct correlation between premethionine fasting homocysteine and mean homocysteine responses during the 24 hours following the methionine load, both before (r = 0.79) and after betaine (r = 0.71). Betaine also increased plasma cysteine levels in patients with the more severe biochemical abnormalities. After betaine there were modest increases in plasma serine (mean increase 25%; P less than 0.025). Since the vascular complications of homocystinuria are related to increased plasma homocysteine, betaine therapy may reduce this risk in patients receiving a

standard pyridoxine and folic acid regimen in whom there are abnormal homocysteine responses after a standard methionine load

Increase in plasma homocysteine associated with parallel increases in plasma S-adenosylhomocysteine and lymphocyte DNA hypomethylation.

Yi P, Melnyk S, Pogribna M, et al.

*J Biol Chem.* 2000 Sep 22; 275(38):29318-23.

S-Adenosylmethionine and S-adenosylhomocysteine (SAH), as the substrate and product of essential cellular methyltransferase reactions, are important metabolic indicators of cellular methylation status. Chronic elevation of SAH, secondary to the homocysteine-mediated reversal of the SAH hydrolase reaction, reduces methylation of DNA, RNA, proteins, and phospholipids. High affinity binding of SAH to the active site of cellular methyltransferases results in product inhibition of the enzyme. Using a sensitive new high pressure liquid chromatography method with coulometric electrochemical detection, plasma SAH levels in healthy young women were found to increase linearly with mild elevation in homocysteine levels ( $r = 0.73$ ;  $p < 0.001$ ); however, S-adenosylmethionine levels were not affected. Plasma SAH levels were positively correlated with intracellular lymphocyte SAH levels ( $r = "0.81;"$   $p < 0.001$ ) and also with lymphocyte DNA hypomethylation ( $r = "0.74,"$   $p < 0.001$ ). These results suggest that chronic elevation in plasma homocysteine levels, such as those associated with nutritional deficiencies or genetic polymorphisms in the folate pathway, may have an indirect and negative effect on cellular methylation reactions through a concomitant increase in intracellular SAH levels

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