

## Polymyalgia Rheumatica

## ABSTRACTS

- Lockwood K., 1994. Apparent partial remission of breast cancer in 'high risk' patients supplemented with nutritional antioxidants, essential fatty acids and coenzyme Q10.
- Lockwood K., 1995. Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases.
- Lord RS., 2002. Estrogen metabolism and the diet-cancer connection: rationale for assessing the ratio of urinary hydroxylated estrogen metabolites.
- Love S. I have heard women talk about using "metronomic dosing" chemotherapy and "COX inhibitors." What are these treatments? Should I try them?
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- Apparent partial remission of breast cancer in 'high risk' patients supplemented with nutritional antioxidants, essential fatty acids and coenzyme Q10.**

Lockwood K, Moesgaard S, Hanioka T, Folkers K. Private Outpatient Clinic, Copenhagen, Denmark.

Mol Aspects Med 1994;15 Suppl:s231-40

Thirty-two typical patients with breast cancer, aged 32-81 years and classified 'high risk' because of tumor spread to the lymph nodes in the axilla, were studied for 18 months following an Adjuvant Nutritional Intervention in Cancer protocol (ANICA protocol). The nutritional protocol was added to the surgical and therapeutic treatment of breast cancer, as required by regulations in Denmark. The added treatment was a combination of nutritional antioxidants (Vitamin C: 2850 mg, Vitamin E: 2500 iu, beta-carotene 32.5 iu, selenium 387 micrograms plus secondary vitamins and minerals), essential fatty acids (1.2 g gamma linolenic acid and 3.5 g n-3 fatty acids) and Coenzyme Q10 (90 mg per day). The ANICA protocol is based on the concept of testing the synergistic effect of those categories of nutritional supplements, including vitamin Q10, previously having shown deficiency and/or therapeutic value as single elements in diverse forms of cancer, as cancer may be synergistically related to diverse biochemical dysfunctions and vitamin deficiencies. Biochemical markers, clinical condition, tumor spread, quality of life parameters and survival were followed during the trial. Compliance was excellent. The main observations were: (1) none of the patients died during the study period. (the expected number was four.) (2) none of the patients showed signs of further distant metastases. (3) quality of life was improved (no weight loss, reduced use of pain killers). (4) six patients showed apparent partial remission.

## **Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases.**

Lockwood K, Moesgaard S, Yamamoto T, Folkers K. Pharma Nord, Vejle, Denmark.

Biochem Biophys Res Commun 1995 Jul 6;212(1):172-7

Over 35 years, data and knowledge have internationally evolved from biochemical, biomedical and clinical research on vitamin Q10 (coenzyme Q10; CoQ10) and cancer, which led in 1993 to overt complete regression of the tumors in two cases of breast cancer. Continuing this research, three additional breast cancer patients also underwent a conventional protocol of therapy which included a daily oral dosage of 390 mg of vitamin Q10 (Bio-Quinone of Pharma Nord) during the complete trials over 3-5 years. The numerous metastases in the liver of a 44-year-old patient "disappeared," and no signs of metastases were found elsewhere. A 49-year-old patient, on a dosage of 390 mg of vitamin Q10, revealed no signs of tumor in the pleural cavity after six months, and her condition was excellent. A 75-year-old patient with carcinoma in one breast, after lumpectomy and 390 mg of CoQ10, showed no cancer in the tumor bed or metastases. Control blood levels of CoQ10 of 0.83-0.97 and of 0.62 micrograms/ml increased to 3.34-3.64 and to 3.77 micrograms/ml, respectively, on therapy with CoQ10 for patients A-MRH and EEL.

## **Estrogen metabolism and the diet-cancer connection: rationale for assessing the ratio of urinary hydroxylated estrogen metabolites.**

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Altern Med Rev 2002 Apr;7(2):112-29

Estrogens are known for their proliferative effects on estrogen-sensitive tissues resulting in tumorigenesis. Results of experiments in multiple laboratories over the last 20 years have shown that a large part of the cancer-inducing effect of estrogen involves the formation of agonistic metabolites of estrogen, especially 16-alpha-hydroxyestrone. Other metabolites, such as 2-hydroxyestrone and 2-hydroxyestradiol, offer protection against the estrogen-agonist effects of 16-alpha-hydroxyestrone. An ELISA method for measuring 2- and 16-alpha-hydroxylated estrogen (OHE) metabolites in urine is available and the ratio of urinary 2-OHE/16-alpha-OHE (2/16-alpha ratio) is a useful biomarker for estrogen-related cancer risk. The CYP1A1 enzyme that catalyzes 2-hydroxyestrone (2-OHE1) formation is inducible by dietary modification and supplementation with the active components of cruciferous vegetables, indole-3-carbinol (I-3-C), or diindolylmethane (DIM). Other dietary components, especially omega-3 polyunsaturated fatty acids and lignans in foods like flax seed, also exert favorable effects on estrogen metabolism. Thus, there appear to be effective dietary means for reducing cancer risk by improving estrogen metabolism. This review presents the accumulated evidence to help clinicians evaluate the merit of using tests that measure estrogen metabolites and using interventions to modify estrogen metabolism.

## **I have heard women talk about using "metronomic dosing" chemotherapy and "COX inhibitors." What are these treatments? Should I try them?** Love, S. (<http://www.susanlovemd.com/community/questions/question010226.htm>).

**The Yam Cream Conundrum 2001 Feb** Lukaczer, D.

([http://www.naturalinvestor.com/nutritionsciencenews/nsn\\_backs/Feb\\_01/counter.cfm](http://www.naturalinvestor.com/nutritionsciencenews/nsn_backs/Feb_01/counter.cfm)).

## **Effect of radiation therapy on small-cell lung cancer is reduced by ubiquinone intake.**

Lund EL, Quistorff B, Spang-Thomsen M, Kristjansen PE. Institute of Molecular Pathology, University of Copenhagen, Denmark.

Folia Microbiol (Praha) 1998;43(5):505-6

The effect of oral ubiquinone (Q10) intake on the in vivo response of tumors to single dose radiotherapy was examined. The human small-cell lung cancer (SCLC) line CPH 054A, which is sensitive to relatively low doses of X-radiation, was grown as subcutaneous transplants in the flanks of nude nu/nu mice. When macroscopical growth was established, groups of mice received either 10, 20 or 40 mg/kg Q10 in 30 mL soy oil intragastrically daily on 4 consecutive days. Controls received either 30 mL of pure soy oil or nothing. Three h after the last dose half of the tumors in each group received a single radiation dose of 5 Gy, using a 300 kV therapeutic unit. The macroscopic growth pre- and posttreatment was analyzed according to a transformed Gompertz algorithm using the software program GROWTH. Treatment with Q10 or soy oil alone had no effect on tumor growth compared with untreated controls. Groups of tumors that received Q10 and radiotherapy had a significantly lower specific growth delay (SGD) than the radiotherapy-only groups. This effect was significant at 40 mg/kg and borderline at 20 mg/kg, whereas at 10 mg/kg no radioprotection was seen. We conclude that systemic Q10 reduces the response to single dose tumor irradiation in xenotransplanted human SCLC tumors.

## **Dietary genistein affects brain protein synthesis rates in ovariectomized female rats.**

Lyou S, Hirano E, Tujioka K, Mawatari Y, Hayase K, Okuyama S, Yokogoshi H. Department of Home Economics, Aichi University of Education, Kariya, Japan.

J Nutr 2002 Jul;132(7):2055-8

The purpose of this study was to determine whether genistein affects the rate of brain protein synthesis in ovariectomized female rats. Experiments were conducted on three groups of 12-wk-old female rats: those in group 1 were ovariectomized to reduce the level of plasma sex hormone; those in group 2 were ovariectomized and fed diets containing 0.01% genistein; and those in group 3 were sham-operated controls. The fractional rates of protein synthesis in the brain of ovariectomized rats fed genistein were significantly greater than those in ovariectomized rats without genistein treatment. In the cerebral cortex and cerebellum, the RNA activity [g protein synthesized/(g RNA.d)] significantly correlated ( $r > 0.86$ ,  $P < 0.001$ ) with the fractional rate of protein synthesis. The RNA concentration (mg RNA/g protein) was not related to the fractional rate of protein synthesis in any organ. The results suggest that the addition of genistein to the diet of ovariectomized female rats is likely to increase the rate of protein synthesis in the brain, and that RNA activity is at least partly related to the fractional rate of brain protein synthesis.

#### **A cost-evaluation of glutamine-supplemented parenteral nutrition in adult bone marrow transplant patients.**

MacBurney M, Young LS, Ziegler TR, Wilmore DW. Nutrition Support Service, Brigham and Women's Hospital, Boston, MA 02115.

J Am Diet Assoc 1994 Nov;94(11):1263-6

**OBJECTIVE:** In a randomized, double-blind, prospective clinical trial, we evaluated the metabolic effects of glutamine-supplemented parenteral nutrition in patients with bone marrow transplants. We compared hospital charge and cost data for the two groups of patients in the trial. **DESIGN:** Retrospective review. **SETTING:** Bone Marrow Transplant Unit, Brigham and Women's Hospital, Boston, Mass. **SUBJECTS:** Forty-three patients admitted to the Bone Marrow Transplant Unit were assigned randomly to receive either standard parenteral nutrition or an isocaloric, isonitrogenous parenteral nutrition solution containing glutamine starting on day 1 after bone marrow transplant. The two groups were well matched for diagnosis, antineoplastic treatment, and sex. **MEASURES:** The primary clinical end points evaluated were nitrogen balance, length of hospitalization, incidence of infection, and results of microbial culture. After completion of the study, we compared the hospital charges for the categories of room and board, surgery, laboratory, pharmacy, radiology, ancillary, and miscellaneous between the two groups of patients. **STATISTICAL ANALYSIS PERFORMED:** The two groups were compared using the unpaired t test or Mann-Whitney test for nonparametric measurements. A P value of  $< .05$  was considered significant. **RESULTS:** Nitrogen balance improved in the glutamine-supplemented group compared with control subjects ( $-1.4 \pm 0.5$  g/day vs  $4.2 \pm 1.2$  g/day, respectively;  $P = .002$ ). Length of hospitalization was significantly shorter in the glutamine-supplemented group than in the control group ( $29 \pm 1$  day vs  $36 \pm 2$  days, respectively;  $P = .017$ ). The incidence of positive microbial cultures and clinical infection was also significantly lower with glutamine supplementation. Hospital charges were \$21,095 per patient less in the glutamine-supplemented group compared with charges for patients who received standard therapy. Room and board charges were significantly different: \$51,484  $\pm$  2,647 for the glutamine-supplemented group vs \$61,591  $\pm$  3,588 in the control group ( $P = .02$ ). **CONCLUSION:** This intervention study using a new therapy demonstrated clinical and nutritional benefits to patients and cost savings to the hospital.

#### **In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress.**

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Biol Psychiatry 2000 May 15;47(10):910-20

**BACKGROUND:** Psychologic stress in humans induces the production of proinflammatory cytokines, such as interferon gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), and interleukin-6 (IL-6), and that of the negative immunoregulatory cytokine, IL-10. An imbalance of omega6 to omega3 polyunsaturated fatty acids (PUFAs) in the peripheral blood causes an overproduction of proinflammatory cytokines. The omega3 PUFAs reduce the production of proinflammatory cytokines. **METHODS:** This study examines whether an imbalance in omega6 to omega3 PUFAs in human blood predicts a greater production of proinflammatory cytokines in response to psychologic stress. Twenty-seven university students had serum sampled a few weeks before and after as well as 1 day before a difficult oral examination. We determined the omega6 and omega3 fractions in serum phospholipids as well as the ex vivo production of IFN-gamma, TNF-alpha, IL-6, IL-10, and IL-5 by diluted whole blood stimulated with polyclonal activators. **RESULTS:** Academic examination stress significantly increased the ex vivo, stimulated production of IFN-gamma, TNF-alpha and IL-10, and the IFN-gamma/IL-5 production ratio. Subjects with lower serum omega3 PUFA levels or with a higher omega6/omega3 ratio had significantly greater stress-induced TNF-alpha and IFN-gamma responses than subjects with higher serum omega3 PUFAs and a lower omega6/omega3 ratio, respectively. Subjects with lower serum omega3 PUFA levels or with a higher omega6/omega3 ratio had a significantly higher stress-induced increase in the IFN-gamma/IL-5 ratio than the remaining

subjects. CONCLUSIONS: Psychologic stress induces a Th-1-like or proinflammatory response in some subjects. An imbalance in the omega6 to omega3 PUFA ratio appears to predispose humans toward an exaggerated Th-1-like response and an increased production of monocytic cytokines, such as TNF-alpha, in response to psychologic stress. The results suggest that increased omega3 PUFA levels may attenuate the proinflammatory response to psychologic stress.

### **Therapeutic potential of melatonin in immunodeficiency states, viral diseases, and cancer.**

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Adv Exp Med Biol 1999;467:217-26

Maintenance of health depends on the ability to respond appropriately to environmental stressors via reciprocal interactions between the body and the brain. In this context, it is well recognized that the pineal hormone melatonin (MLT) plays an important role. T-helper cells bear G-protein-coupled MLT cell membrane receptors and, perhaps, MLT nuclear receptors. Activation of MLT receptors enhances the release of T-helper cell cytokines, such as gamma-interferon and interleukin-2 (IL-2), as well as activation of novel opioid cytokines which crossreact immunologically with both interleukin-4 and dynorphin B. MLT has been reported also to enhance the production of interleukin-1, interleukin-6 and interleukin-12 in human monocytes. These mediators may counteract secondary immunodeficiencies, protect mice against lethal viral and bacterial diseases, synergize with IL-2 against cancer and influence hematopoiesis. Hematopoiesis is influenced by MLT-induced-opioids (MIO) acting on kappa 1-opioid receptors present on bone marrow macrophages. Clinically, MLT could amplify the anti-tumoral activity of low dose IL-2, induce objective tumor regression, and prolong progression-free time and overall survival. MLT seems to be required for the effectiveness of low dose IL-2 in those neoplasias that are generally resistant to IL-2 alone. Similar findings were obtained in a study in which MLT was combined with gamma-interferon in metastatic renal cell carcinoma. In addition, MLT in combination with low-dose IL-2 was able to neutralize the surgery-induced lymphocytopenia in cancer patients. IL-2 treatment in patients results in activation of the immune system and creates the most suitable biological background for MLT. The finding that MLT stimulates IL-12 production from human monocytes only if incubated in presence of IL-2 further supports this concept. On the other hand, high concentrations of MLT have been found in human breast cancer tissue. The MLT concentration, which was 3 orders of magnitude higher than that present in the plasma, correlated positively with good prognostic markers such as estrogen receptor status and nuclear grade. Whether this relates to the immunoneuroendocrine action of MLT remains to be established. Clinical studies are needed on the effect of MLT in combination with IL-2 or other cytokines in cancer patients and viral diseases including HIV-infected patients.

### **The immunotherapeutic potential of melatonin.**

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Expert Opin Investig Drugs 2001 Mar;10(3):467-76

The interaction between the brain and the immune system is essential for the adaptive response of an organism against environmental challenges. In this context, the pineal neurohormone melatonin (MEL) plays an important role. T-helper cells express G-protein coupled cell membrane MEL receptors and, perhaps, MEL nuclear receptors. Activation of MEL receptors enhances the release of T-helper cell Type 1 (Th1) cytokines, such as gamma-interferon (gamma-IFN) and IL-2, as well as of novel opioid cytokines. MEL has been reported also to enhance the production of IL-1, IL-6 and IL-12 in human monocytes. These mediators may counteract stress-induced immunodepression and other secondary immunodeficiencies and protect mice against lethal viral encephalitis, bacterial diseases and septic shock. Therefore, MEL has interesting immunotherapeutic potential in both viral and bacterial infections. MEL may also influence haemopoiesis either by stimulating haemopoietic cytokines, including opioids, or by directly affecting specific progenitor cells such as pre-B cells, monocytes and NK cells. MEL may thus be used to stimulate the immune response during viral and bacterial infections as well as to strengthen the immune reactivity as a prophylactic procedure. In both mice and cancer patients, the haemopoietic effect of MEL may diminish the toxicity associated with common chemotherapeutic protocols. Through its pro-inflammatory action, MEL may play an adverse role in autoimmune diseases. Rheumatoid arthritis patients have increased nocturnal plasma levels of MEL and their synovial macrophages respond to MEL with an increased production of IL-12 and nitric oxide (NO). In these patients, inhibition of MEL synthesis or use of MEL antagonists might have a therapeutic effect. In other diseases such as multiple sclerosis the role of MEL is controversial. However, the correct therapeutic use of MEL or MEL antagonists should be based on a complete understanding of their mechanism of action. It is not yet clear whether MEL acts only on Th1 cells or also on T-helper Type 2 cells (Th2). This is an important point as the Th1/Th2 balance is of crucial importance in the immune system homeostasis. Furthermore, MEL being the endocrine messenger of darkness, its endogenous synthesis depends on the photoperiod and shows seasonal variations. Similarly, the pharmacological effects of MEL might also be season-dependent. No information is available concerning this point. Therefore, studies are needed to investigate whether the immunotherapeutic effect of MEL changes with the alternating seasons.

### **N-3 and N-6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case-control study in Tours,**

## France.

Maillard V, Bougnoux P, Ferrari P, Jourdan ML, Pinault M, Lavillonniere F, Body G, Le Floch O, Chajes V. Laboratoire de Biologie des Tumeurs, Clinique d'Oncologie-Radiotherapie, Service de Gynecologie-Obstetrique, E.A. 2103, Unite de Recherche Associee Universite-INRA, CHU, Tours, France.

Int J Cancer 2002 Mar 1;98(1):78-83

Experimental studies have indicated that n-3 fatty acids, including alpha-linolenic acid (18:3 n-3) and long-chain n-3 polyunsaturated fatty acids inhibit mammary tumor growth and metastasis. Earlier epidemiological studies have given inconclusive results about a potential protective effect of dietary n-3 polyunsaturated fatty acids on breast cancer risk, possibly because of methodological issues inherent to nutritional epidemiology. To evaluate the hypothesis that n-3 fatty acids protect against breast cancer, we examined the fatty acid composition in adipose tissue from 241 patients with invasive, nonmetastatic breast carcinoma and from 88 patients with benign breast disease, in a case-control study in Tours, central France. Fatty acid composition in breast adipose tissue was used as a qualitative biomarker of past dietary intake of fatty acids. Biopsies of adipose tissue were obtained at the time of surgery. Individual fatty acids were measured as a percentage of total fatty acids, using capillary gas chromatography. Unconditional logistic regression modeling was used to obtain odds ratio estimates while adjusting for age, height, menopausal status and body mass index. We found inverse associations between breast cancer-risk and n-3 fatty acid levels in breast adipose tissue. Women in the highest tertile of alpha-linolenic acid (18:3 n-3) had an odds ratio of 0.39 (95% confidence intervals [CI] = 0.19-0.78) compared to women in the lowest tertile (trend  $p = 0.01$ ). In a similar way, women in the highest tertile of docosahexaenoic acid (22:6 n-3) had an odds ratio of 0.31 (95% CI = 0.13-0.75) compared to women in the lowest tertile (trend  $p = 0.016$ ). Women in the highest tertile of the long-chain n-3/total n-6 ratio had an odds ratio of 0.33 (95% confidence interval = 0.17-0.66) compared to women in the lowest tertile (trend  $p = 0.0002$ ). In conclusion, our data based on fatty acids levels in breast adipose tissue suggest a protective effect of n-3 fatty acids on breast cancer risk and support the hypothesis that the balance between n-3 and n-6 fatty acids plays a role in breast cancer. Copyright 2001 Wiley-Liss, Inc.

## Vitamin E inhibits melanoma growth in mice.

Malafa MP, Fokum FD, Mowlavi A, Abusief M, King M. Department of Surgery, Southern Illinois University School of Medicine, Springfield, IL 62794-9638, USA.

Surgery 2002 Jan;131(1):85-91

**BACKGROUND:** Previous work has demonstrated that vitamin E succinate (VES), an ester analogue of vitamin E, inhibits the growth of melanoma in vitro. However, there is no information about the effect of VES on melanoma in vivo. We investigated the effect of VES on melanoma in vitro and in vivo. **METHODS:** The effect of VES on the proliferation and apoptosis of the B16F10 murine melanoma cell line was determined by a modified Cell Titer 96 AQ assay and a cell death detection enzyme-linked immunosorbent assay, respectively. The in vivo effect of VES on B16F10 melanoma cells allografted in athymic nude mice was investigated. The mechanism of the in vivo antitumor effect of VES was determined by immunohistochemical detection of proliferation and apoptosis. **RESULTS:** VES decreased cell proliferation ( $P = .0001$ ) and increased cell apoptosis ( $P = .0001$ ) in a dose-dependent manner in vitro. Also, VES significantly inhibited melanoma growth in mice ( $P = .0013$ ). The VES antitumor effect in vivo was associated with a significant increase in the melanoma apoptosis rate ( $P = .0256$ ). **CONCLUSIONS:** This is the first report of the antimelanoma effect of VES in vivo. The mechanism of the antimelanoma effect of VES in vivo involves the promotion of tumor cell apoptosis. These findings support future investigations of VES as a therapeutic micronutrient against melanoma.

## Prospective study of serum selenium levels and incident esophageal and gastric cancers.

Mark SD, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, Fraumeni JF Jr, Blot WJ, Dong ZW, Taylor PR.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institute of Health, Bethesda, MD 20852-4910, USA.

J Natl Cancer Inst 2000 Nov 1;92(21):1753-63

**BACKGROUND:** From March 1986 through May 1991, we conducted a randomized nutritional intervention trial, the General Population Trial, in Linxian, China, a region with epidemic rates of squamous esophageal and adenomatous gastric cardia cancers. We found that participants who received selenium, beta-carotene, and vitamin E had significantly lower cancer mortality rates than those who did not. In the current study, we examined the relationship between selenium levels measured in pretrial (1985) sera from participants and the subsequent risk of developing squamous esophageal, gastric cardia, and gastric non-cardia cancers during the trial. **METHODS:** This study was designed and analyzed in accord with a stratified case-cohort sampling scheme, with the six strata defined by sex and three age categories. We measured serum selenium levels in 590 case subjects with esophageal cancer, 402 with gastric cardia cancers, and 87 with gastric non-cardia cancers as well as in 1062 control subjects. Relative risks (RRs),

absolute risks, and population attributable risk for cancers were estimated on the basis of the Cox proportional hazards models. All statistical tests are two-sided. RESULTS: We found highly significant inverse associations of serum selenium levels with the incidence of esophageal (P: for trend <10<sup>-4</sup>) and gastric cardia (P: for trend <10<sup>-6</sup>) cancers. The RR and 95% confidence interval (CI) for comparison of highest to lowest quartile of serum selenium was 0.56 (95% CI = 0.44-0.71) for esophageal cancer and 0.47 (95% CI = 0.33-0.65) for gastric cardia cancer. The population proportion of these cancers that is attributable to low selenium levels was 26.4% (95% CI = 14.45-38.36). We found no evidence for a gradient of serum selenium associated with incidence of gastric non-cardia cancer (P: for trend =.96), with an RR of 1.07 (95% CI = 0.55-2.08) for the highest to lowest quartile of serum selenium. CONCLUSIONS: Our study supports findings from previous prospective studies and randomized trials that variations in selenium levels affect the incidence of certain cancers. In the United States, where intervention trials of selenium are in the planning stages, consideration should be given to including populations at high risk for squamous esophageal and gastric cardia cancers.

#### **Effects of combinations of therapeutic agents on the proliferation of progenitor cells in chronic myeloid leukaemia.**

Marley SB, Davidson RJ, Goldman JM, Gordon MY. Leukaemia Research Fund Centre for Adult Leukaemia, Department of Haematology, Imperial College School of Medicine, London, UK. s.marley@ic.ac.uk

Br J Haematol 2002 Jan;116(1):162-5

Combination of STI571, a tyrosine kinase inhibitor, with other drugs may be beneficial in the treatment of chronic myeloid leukaemia (CML). We measured the effects of STI571, AG490, farnesyltransferase inhibitor (FTI), interferon alpha (IFN-alpha), cytosine arabinoside (Ara-C) and all-trans retinoic acid (ATRA), singly and in combination, on clonogenic leukaemic cell proliferation. STI571, IFN-alpha and ATRA each reduced proliferation by 50-60%; AG490, FTI and Ara-C had less effect. Comparing the observed and expected (i.e. additive) effects of drug combinations showed STI571 + FTI, STI571 + AG490 and IFN-alpha + ATRA were additive; STI571 + IFN-alpha, IFN-alpha + Ara-C and STI571 + AG490 + FTI were less than additive. Thus, STI571 + FTI, STI571 + AG490 and IFN-alpha + ATRA may be better combination therapies for CML than STI571 + IFN-alpha, IFN-alpha + Ara-C or STI571 + AG490 + FTI.

#### **Genetic and hormonal risk factors in breast cancer.**

Martin AM, Weber BL. Department of Medicine, Division of Hematology and Oncology, University of Pennsylvania, Philadelphia 19104, USA.

J Natl Cancer Inst 2000 Jul 19;92(14):1126-35

Breast cancer poses a serious public health problem, and it is hoped that identification of genetic and environmental factors that contribute to the development of breast cancer will enhance prevention efforts. Two breast cancer susceptibility genes (BRCA1 and BRCA2) have been identified, and germline mutations in these genes are thought to account for between 5% and 10% of all breast cancer cases. Current findings suggest that mutations in other highly penetrant genes may play an important role in breast cancer susceptibility, and studies aimed at the isolation of these genes are under way. In addition, common variants in a number of gene classes are thought to act as low-penetrance susceptibility alleles, and efforts to identify and characterize these variants are under way. This review discusses the genetic components of susceptibility to breast cancer from the standpoint of both human genetics and rat models.

#### **Chemopreventive effects of bovine lactoferrin on N-butyl-N-(4-hydroxybutyl)nitrosamine-induced rat bladder carcinogenesis.**

Masuda C, Wanibuchi H, Sekine K, Yano Y, Otani S, Kishimoto T, Tsuda H, Fukushima S. Department of Pathology, Osaka City University Medical School, Abeno-ku, Osaka 545-8585, Japan.

Jpn J Cancer Res 2000 Jun;91(6):582-8

Chemopreventive effects of bovine lactoferrin (bLF), which is found at high concentrations in colostrum, on rat bladder carcinogenesis were investigated using a rat bladder medium-term bioassay. In experiment 1, a total of 80 F344 male rats, 6 weeks old, were divided into 5 groups. Groups 1 and 2 were treated with 0.05% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) in the drinking water for 8 weeks and after a 1-week interval, received dietary supplementation with 2% and 0.2% bLF, respectively. Group 3 received 0.05% BBN for 8 weeks and then no treatment. Group 4 was administered 2% bLF alone from week 9, without prior carcinogen exposure. Group 5 was maintained without any treatment throughout the experiment. All rats were killed at the end of week 36. Group 1 demonstrated a significantly decreased multiplicity of the bladder tumors (carcinomas and papillomas) as compared with group 3. Maximum cut surface areas of bladder tumors were also significantly decreased in groups 1 and 2.

compared with group 3. No bladder tumors were observed in groups 4 or 5. In experiment 2, a total of 60 rats were divided into two groups (30 rats each); both were treated with 0.05% BBN for 4 weeks and after a 1-week interval, one received 2% bLF (group 1) and the other, basal diet (group 2) for 4 weeks. Group 1 demonstrated a tendency for decrease of the 5-bromo-2'-deoxyuridine (BrdU) labeling index. bLF was detected in the urine of rats fed bLF by ELISA as well as western blot analysis. The findings indicate that 2% bLF can inhibit BBN-induced rat bladder carcinogenesis, and that this may be due to bLF in the urine.

### **Cimetidine increases survival of colorectal cancer patients with high levels of sialyl Lewis-X and sialyl Lewis-A epitope expression on tumour cells.**

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Br J Cancer 2002 Jan 21;86(2):161-7

Cimetidine has been shown to have beneficial effects in colorectal cancer patients. In this study, a total of 64 colorectal cancer patients who received curative operation were examined for the effects of cimetidine treatment on survival and recurrence. The cimetidine group was given 800 mg day<sup>-1</sup> of cimetidine orally together with 200 mg day<sup>-1</sup> of 5-fluorouracil, while the control group received 5-fluorouracil alone. The treatment was initiated 2 weeks after the operation and terminated after 1 year. Robust beneficial effects of cimetidine were noted: the 10-year survival rate of the cimetidine group was 84.6% whereas that of control group was 49.8% (P<0.0001). According to our previous observations that cimetidine blocked the expression of E-selectin on vascular endothelium and inhibited the adhesion of cancer cells to the endothelium, we have further stratified the patients according to the expression levels of sialyl Lewis antigens X (sL(x)) and A (sL(a)). We found that cimetidine treatment was particularly effective in patients whose tumour had higher sL(x) and sL(a) antigen levels. For example, the 10-year cumulative survival rate of the cimetidine group with higher CSLEX staining, recognizing sL(x), of tumours was 95.5%, whereas that of control group was 35.1% (P=0.0001). In contrast, in the group of patients with no or low levels CSLEX staining, cimetidine did not show significant beneficial effect (the 10-year survival rate of the cimetidine group was 70.0% and that of control group was 85.7% (P=n.s.)). These results clearly indicate that cimetidine treatment dramatically improved survival in colorectal cancer patients with tumour cells expressing high levels of sL(x) and sL(a). Copyright 2002 The Cancer Research Campaign

**MGN-3: cure or curiosity? The question persists!** McAllister, E. Well Being Journal, Special Edition 2001.

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(<http://inq.philly.com/content/inquirer/2001/10/22/magazine/FREQUENCY22.htm>).

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**How You Can Beat Prostate and Breast Cancer Nutritionally 2000** Mercola, J.  
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**Omega-3 Fats Prevent Breast Cancer 2002** Mercola, J. (<http://www.mercola.com/2002/mar/23/omega3.htm>).

### **Gaining insight into the health effects of soy but a long way still to go: commentary on the fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease.**

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J Nutr 2002 Mar;132(3):547S-551S

Research into the health effects of soyfoods and soybean constituents has increased at a phenomenal pace over the past decade. This research includes a wide range of areas, such as cancer, coronary heart disease, osteoporosis, cognitive function, menopausal symptoms and renal function. Importantly, there are an increasing number of clinical studies being conducted in this field, which was quite evident from the findings presented at the Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, November 4-7, 2001, in San Diego, California. There is no doubt that progress in understanding the health effects of soy is being made, but much of the data are frustratingly inconsistent. For example, there were conflicting results presented at the symposium on the role of isoflavones in bone health. Similarly, presentations painted an unclear picture of the role of isoflavones in cholesterol reduction. The relatively short duration and small sample size of many of the human studies in this field likely contribute to the inconsistent results. Although there are some controversies regarding the safety of soy for certain subsets of the population, special sessions at the symposium on breast cancer and cognitive function did much to alleviate concerns that soy could have detrimental effects in these areas. Furthermore, published data and new research presented at this meeting suggest that

the consumption of even 10 g (typical of Asian intake) of isoflavone-rich soy protein per day may be associated with health benefits. If this modest amount of soy protein were to be incorporated in the American diet, it would represent only approximately 15% of total U. S. protein intake.

### **Modulation of arachidonic acid distribution by conjugated linoleic acid isomers and linoleic acid in MCF-7 and SW480 cancer cells.**

Miller A, Stanton C, Devery R. School of Biotechnology, Dublin City University, Dublin, Ireland.

Lipids 2001 Oct;36(10):1161-8

The relationship between growth and alterations in arachidonic acid (AA) metabolism in human breast (MCF-7) and colon (SW480) cancer cells was studied. Four different fatty acid preparations were evaluated: a mixture of conjugated linoleic acid (CLA) isomers (c9,t11, t10,c12, c11,t13, and minor amounts of other isomers), the pure c9,t11-CLA isomer, the pure t10,c12-CLA isomer, and linoleic acid (LA) (all at a lipid concentration of 16 microg/mL). 14C-AA uptake into the monoglyceride fraction of MCF-7 cells was significantly increased following 24 h incubation with the CLA mixture ( $P < 0.05$ ) and c9,t11-CLA ( $P < 0.02$ ). In contrast to the MCF-7 cells, 14C-AA uptake into the triglyceride fraction of the SW480 cells was increased while uptake into the phospholipids was reduced following treatment with the CLA mixture ( $P < 0.02$ ) and c9,t11-CLA ( $P < 0.05$ ). Distribution of 14C-AA among phospholipid classes was altered by CLA treatments in both cell lines. The c9,t11-CLA isomer decreased ( $P < 0.05$ ) uptake of 14C-AA into phosphatidylcholine while increasing ( $P < 0.05$ ) uptake into phosphatidylethanolamine in both cell lines. Both the CLA mixture and the t10,c12-CLA isomer increased ( $P < 0.01$ ) uptake of 14C-AA into phosphatidylserine in the SW480 cells but had no effect on this phospholipid in the MCF-7 cells. Release of 14C-AA derivatives was not altered by CLA treatments but was increased ( $P < 0.05$ ) by LA in the SW480 cell line. The CLA mixture of isomers and c9,t11-CLA isomer inhibited 14C-AA conversion to 14C-prostaglandin E2 (PGE2) by 20-30% ( $P < 0.05$ ) while increasing 14C-PGF2alpha by 17-44% relative to controls in both cell lines. LA significantly ( $P < 0.05$ ) increased 14C-PGD2 by 13-19% in both cell lines and increased 14C-PGE2 by 20% in the SW480 cell line only. LA significantly ( $P < 0.05$ ) increased 5-hydroperoxyeicosatetraenoate by 27% in the MCF-7 cell line. Lipid peroxidation, as determined by increased levels of 8-epi-prostaglandin F2alpha (8-epi-PGF2alpha), was observed following treatment with c9,t11-CLA isomer in both cell lines ( $P < 0.02$ ) and with t10,c12-CLA isomer in the MCF-7 cell line only ( $P < 0.05$ ). These data indicate that the growth-promoting effects of LA in the SW480 cell line may be associated with enhanced conversion of AA to PGE2 but that the growth-suppressing effects of CLA isomers in both cell lines may be due to changes in AA distribution among cellular lipids and an altered prostaglandin profile.

### **A protein fraction from aged garlic extract enhances cytotoxicity and proliferation of human lymphocytes mediated by interleukin-2 and concanavalin A.**

Morioka N, Sze LL, Morton DL, Irie RF. Division of Surgical Oncology, UCLA School of Medicine 90024.

Cancer Immunol Immunother 1993 Oct;37(5):316-22

Fraction 4 (F4), a protein fraction isolated from aged garlic extract, enhanced cytotoxicity of human peripheral blood lymphocytes (PBL) against both natural-killer (NK)-sensitive K562 and NK-resistant M14 cell lines. Although F4 treatment alone increased cytotoxicity, the effect was more remarkable when F4 was administered together with suboptimal doses of interleukin-2 (IL-2); combination treatment of 5 micrograms/ml F4 plus 10 U/ml IL-2 for 72 h generated lymphokine-activated killer activity equivalent to that produced by 100 U/ml IL-2 alone against M14. F4 enhanced IL-2-induced proliferation and IL-2 receptor (Tac) expression of PBL without significant increase of IL-2 production. The enhancement of cytotoxicity both by F4 alone and by F4 plus IL-2 was abolished by anti-IL-2 antibody. F4 also enhanced concanavalin-A(ConA)-induced proliferation of PBL. Radiolabeled-ConA binding assays revealed that F4 treatment greatly augmented the affinity and slightly increased the number of ConA binding sites in PBL. F4 also enhanced ConA-induced IL-2 receptor (Tac) expression and IL-2 production of PBL. Anti-IL-2 antibody inhibited the effect of F4 on ConA-induced proliferation. These data suggest that IL-2 is involved in augmentative effects of F4. Our results indicate that F4 is a very efficient immunopotentiator and may be used for immunotherapy.

**Melatonin vs. cancer.** Moss, R. Cancer Chronicles #27 1995 May (<http://www.ralphmoss.com/melatonin.html>).

**Antioxidants Against Cancer 2000.** Moss, R. Brooklyn, NY: Equinox Press.

### **S-allylcysteine ameliorates doxorubicin toxicity in the heart and liver in mice.**

Mostafa MG, Mima T, Ohnishi ST, Mori K. Department of Neurosurgery, Kochi Medical School, Japan.

Planta Med 2000 Mar;66(2):148-51

Doxorubicin, a potent anticancer drug, is effective against a wide range of human neoplasms. However, the clinical uses of doxorubicin have been limited due to its serious cardiotoxic effects, which are likely the result of generation of free radicals and lipid peroxidation. S-Allylcysteine (SAC), an organosulfur compound purified from garlic, has been reported to have antioxidant and radical scavenging effects. Thus, we examined the effect of SAC on doxorubicin toxicity in mice. Severe doxorubicin toxicity was induced in mice by a single intraperitoneal injection (15 mg/kg body weight). SAC (30 mg/kg) was injected intraperitoneally daily for 5 days, starting two days prior to the administration of doxorubicin. Body weight was measured every alternate day. A measurement of serum creatine phosphokinase (CPK) and a histopathological analysis of the heart and liver was performed 6 days after the administration of doxorubicin. Death of any of the animals was recorded during the observation period. Doxorubicin injection induced a mortality rate of 58%, with SAC treatment reducing the doxorubicin-induced mortality rate to 30%. The severe body weight loss caused by doxorubicin (13%) was also significantly attenuated by SAC treatment (9%). Although an elevation of the level of serum CPK was observed following doxorubicin injection (5472 +/- 570 i.u./L), treatment with SAC significantly reduced the level of CPK (1923 +/- 635 i.u./L). Histological analysis demonstrated that heart and liver damage was significantly less severe in SAC treated mice than in mice receiving only doxorubicin. These results suggest that SAC research may ultimately lead to a resolution of the adverse effects of doxorubicin treatment in cancer chemotherapy.

### **Arginine induces apoptosis and gene expression of pancreatitis-associated protein (PAP) in rat pancreatic acinar AR4-2J cells.**

Motoo Y, Taga K, Su SB, Xie MJ, Sawabu N. Department of Internal Medicine and Medical Oncology, Cancer Research Institute, Kanazawa University, Japan. [motoo@kenroku.kanazawa-u.ac.jp](mailto:motoo@kenroku.kanazawa-u.ac.jp)

Pancreas 2000 Jan;20(1):61-6

Arginine-induced pancreatic acinar cell injury has been reported in vivo, but the mechanism involved is unknown. In this study we investigated the effects of arginine on the cell morphology and pancreatitis-associated protein (PAP) gene expression in rat pancreatic acinar AR4-2J cells in vitro. Arginine inhibited the proliferation of AR4-2J cells in a dose-dependent manner. This decrease in proliferation was due to an increase in apoptosis, as assessed by cell morphology and DNA fragmentation. PAP messenger RNA (mRNA) was expressed at doses of 2.5 and 5.0 mg/ml of arginine, and a time-course study showed that the expression started 2 h after arginine addition and peaked at 6 h. Apoptosis was rarely seen when PAP mRNA was highly expressed, but occurred when PAP mRNA expression was decreased. These results suggest that arginine induces apoptosis and PAP gene expression in pancreatic acinar cells and that PAP might inhibit the induction of apoptosis.

### **Vitamin E, alpha- and gamma-tocopherol, and prostate cancer.**

Moyad MA, Brumfield SK, Pienta KJ. Section of Urology, University of Michigan, Ann Arbor 48109-0330, USA.

Semin Urol Oncol 1999 May;17(2):85-90

Vitamin E is one of the most researched compounds in medicine. Vitamin E is actually a general name for potentially eight different compounds, so supplements can contain several forms and vitamin E in the diet also differs from the form found over the counter. There has been a strong interest in this supplement in the prostate cancer arena primarily because of a Finnish study that demonstrated a lower morbidity and mortality from this disease in men taking 50 mg of synthetic (alpha-tocopherol) vitamin E daily. In addition, observations from laboratory and clinical studies dealing with heart disease have found that gamma-tocopherol may also play a significant role in prevention; therefore, we decided to test the ability of this compound (versus synthetic vitamin E) to control the growth of a human prostate cancer cell line. Gamma-tocopherol was found to be superior to alpha-tocopherol in terms of cell inhibition in vitro. Both forms of vitamin E (and others) should be thoroughly evaluated in the future to provide the most effective chemoprevention information to the patient.

### **Effects of arginine, L-alanyl-L-glutamine or taurine on neutrophil (PMN) free amino acid profiles and immune functions in vitro.**

Muhling J, Fuchs M, Fleck C, Sablotzki A, Krull M, Dehne MG, Gonter J, Weiss S, Engel J, Hempelmann G. Department of Anaesthesiology and Intensive Care Medicine, Justus Liebig University, Giessen, Federal Republic of Germany. [joerg.muehling@chiru.med.uni-giessen.de](mailto:joerg.muehling@chiru.med.uni-giessen.de)

Amino Acids 2002;22(1):39-53

The objective of this study was to determine the effects of arginine, L-alanyl-L-glutamine (Ala-Gln) or taurine on polymorphonuclear leucocyte (PMN) free amino acid profiles, superoxide anion (O<sub>2</sub><sup>-</sup>) generation, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) formation and released myeloperoxidase activity (MPO). Arginine led to significant increases in PMN arginine, ornithine, citrulline, aspartate, glutamate and alanine concentrations as well as increased H<sub>2</sub>O<sub>2</sub>-generation and MPO activity while O<sub>2</sub><sup>-</sup>-formation was decreased. Ala-Gln caused significant increases in PMN free glutamine, alanine, asparagine, aspartate, glutamate, ornithine, arginine, serine and

glycine concentrations and increased PMN immune functions. Taurine significantly increased PMN free taurine profiles, reduced PMN neutral amino acid content and decreased H<sub>2</sub>O<sub>2</sub>- and O<sub>2</sub><sup>-</sup>-formation while MPO was increased. Altogether, the pharmacological regimens which enhance the supply of arginine, Ala-Gln or taurine in whole blood significantly affect PMN "susceptible free amino acid pool". This may be one of the determinants in PMN nutrition considerably influencing PMN immune functions. Introduction Polymorphonuclear leucocytes (PMN) ensure an important part of non-specific cell-mediated immunity and play a crucial role in the host defense

### **Hypoxic induction of human vascular endothelial growth factor expression through c-Src activation.**

Mukhopadhyay D, Tsiokas L, Zhou XM, Foster D, Brugge JS, Sukhatme VP. Beth Israel Hospital, Boston, Massachusetts 02215, USA.

Nature 1995 Jun 15;375(6532):577-81

Angiogenesis, the formation of new microvasculature by capillary sprouting, is crucial for tumour development. Hypoxic regions of solid tumours produce the powerful and directly acting angiogenic protein VEGF/VPF (vascular endothelial growth factor/vascular permeability factor). We now investigate the signal transduction pathway involved in hypoxic induction of VEGF expression. Hypoxia is known to induce a tyrosine kinase cascade that results in the activation of nitrogen-fixation genes in *Rhizobium meliloti*, and activation of tyrosine kinases is critical in signalling triggered by growth factors and ultraviolet light. We show here that genistein, an inhibitor of protein tyrosine kinase, blocks VEGF induction. Hypoxia increases the kinase activity of pp60c-src and its phosphorylation on tyrosine 416 but does not activate Fyn or Yes. Expression of either a dominant-negative mutant form of c-Src or of Raf-1 markedly reduces VEGF induction. VEGF induction by hypoxia in c-src(-) cells is impaired, although there is a compensatory activation of Fyn. Our results provide an insight into hypoxia-triggered intracellular signalling, define VEGF as a new downstream target for c-SRC, and suggest a role for c-SRC in promoting angiogenesis.

### **Pyrrrolidine dithiocarbamate inhibits the production of interleukin-6, interleukin-8, and granulocyte-macrophage colony-stimulating factor by human endothelial cells in response to inflammatory mediators: modulation of NF-kappa B and AP-1 transcription factors activity.**

Munoz C, Pascual-Salcedo D, Castellanos MC, Alfranca A, Aragonés J, Vara A, Redondo MJ, de Landazuri MO. Servicio de Inmunología, Hospital de la Princesa, Universidad Autónoma de Madrid, Spain.

Blood 1996 Nov 1;88(9):3482-90

Endothelial cells (EC) play a key role in the inflammatory response, both by the production of proinflammatory cytokines and by their interaction with leukocytes. Molecular genetic analysis has demonstrated that functional NF-kappa B sites are involved in the transcription of interleukin-6 (IL-6), IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) genes in response to inflammatory mediators. Thus, we have explored the effect of two inhibitors of the NF-kappa B activation, pyrrolidine dithiocarbamate (PDTC) and N-acetylcysteine (NAC), on the production of these cytokines by EC. Both PDTC and NAC inhibited, in a dose-dependent manner, the synthesis of IL-6, IL-8, and GM-CSF induced by tumor necrosis factor (TNF)-alpha or bacterial lipopolysaccharides (LPS) in human umbilical vein endothelial cells (HUVEC). PDTC appeared to prevent IL-6, IL-8, and GM-CSF gene transcription, as it blocked the induction of specific mRNA by TNF-alpha or LPS. The TNF-alpha mediated transcriptional activation of a chloramphenicol acetyltransferase (CAT) plasmid containing three copies of the -72 kappa B binding site from the IL-6 promoter was abrogated by PDTC. According to transfection experiments, electrophoretic mobility shift assays (EMSA) demonstrated that the antioxidant prevented the induction of NF-kappa B DNA-binding activity by TNF-alpha. Under the same conditions, PDTC by itself or in combination with TNF-alpha, enhanced the DNA-binding activity of AP-1, as well as c-fos and c-jun mRNA levels. Altogether, these results indicate that the antioxidant PDTC specifically inhibits the transcription of IL-6, IL-8, and GM-CSF genes through the inhibition of the NF-kappa B activation, while increasing the expression of AP-1. Our data make evident the antiinflammatory and immunoregulatory potential of the pharmacological inhibition of the NF-kappa B activation. In addition, PDTC and related molecules may be a useful tool to explore the expression of genes involved in the inflammatory response.

### **A secreted/shed product of Helicobacter pylori activates transcription factor nuclear factor-kappa B.**

Munzenmaier A, Lange C, Glocker E, Covacci A, Moran A, Bereswill S, Baeuerle PA, Kist M, Pahl HL. Institute for Experimental Cancer Research, Tumor Biology Center, Freiburg, Germany.

J Immunol 1997 Dec 15;159(12):6140-7

*Helicobacter pylori* is an etiologic agent in the development of chronic gastritis, duodenal ulceration, and gastric adenocarcinoma. Exposure of gastric epithelial cells to *H. pylori* induces secretion of the cytokine IL-8, which plays a pivotal role in the immunopathogenesis of *H. pylori* infections. Isolated *Helicobacter* strains differ in their virulence and in their ability to induce cytokine production. High degrees of virulence correlate with enhanced IL-8 production. However, the molecular mechanism of this

variance in Helicobacter pathogenicity remains poorly understood. Here we show that H. pylori-mediated IL-8 secretion requires activation of the transcription factor nuclear factor-kappaB (NF-kappaB) in a gastric epithelial cell line. Several H. pylori strains which fail to induce IL-8 secretion do not activate NF-kappaB, while all IL-8-inducing strains activate the transcription factor. Moreover, the antioxidant curcumin, which inhibits NF-kappaB activation, also completely suppresses IL-8 induction by H. pylori. NF-kappaB activation is not mediated by LPSs, since purified H. pylori LPS had no effect on gastric epithelial cells. In contrast, both IL-8 secretion and NF-kappaB activation require a secreted H. pylori product, which is not secreted by strains mutated in picB/cagE, a recently identified putative transport protein.

**Melatonin in feverfew and other medicinal plants.** Murch SJ, Simmons CB, Saxena PK. Lancet 1997 Nov 29; 350(9091): 1598-9. No Abstract

**Encyclopedia of Nutritional Supplements** Murray, M. 1996, p. 197 (Chromium). Petaluma, CA: Prima Publishing.

**Encyclopedia of Natural Medicine** Murray, M., Pizzorno, J. 1991, pp. 670-8. Petaluma, CA: Prima Publishing.

**Telomerase inhibition, telomere shortening, and senescence of cancer cells by tea catechins.**

Naasani I, Seimiya H, Tsuruo T. Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Kami-Ikebukuro, Tokyo, Toshima-ku, 170-8455, Japan. inaasani@ns.jfcr.or.jp

Biochem Biophys Res Commun 1998 Aug 19;249(2):391-6

Animal in vivo studies and human epidemiological observations indicated potent anticancer effects for tea. Here we demonstrate that epigallocatechin gallate (EGCG), a major tea catechin, strongly and directly inhibits telomerase, an enzyme essential for unlocking the proliferative capacity of cancer cells by maintaining the tips of their chromosomes. Telomerase inhibition was elaborated in a cell-free system (cell extract) as well as in living cells. In addition, the continued growth of two representative human cancer cell lines, U937 monoblastoid leukemia cells and HT29 colon adenocarcinoma cells, in the presence of nontoxic concentrations of EGCG showed life span limitations accompanied with telomere shortening, chromosomal abnormalities, and expression of the senescence-associated beta-galactosidase. It is suggested that telomerase inhibition could be one of the major mechanisms underlying the anticancer effects of tea. Copyright 1998 Academic Press.

**Inhibition of in vitro tumor cell-endothelial adhesion by modified citrus pectin: a pH modified natural complex carbohydrate.** Naik, H. et al. Proc. Am. Assoc. Cancer Res. 1995; 36(Abstr. 377).

**Serum and colon mucosa micronutrient antioxidants: differences between adenomatous polyp patients and controls.**

Nair S, Norkus EP, Hertan H, Pitchumoni CS. Division of Gastroenterology, Our Lady of Mercy Medical Center and New York Medical College, Bronx 10466, USA.

Am J Gastroenterol 2001 Dec;96(12):3400-5

**OBJECTIVES:** Micronutrient antioxidants, by virtue of their free radical scavenging properties, are potential chemopreventive agents against colon cancer. Yet, little is known about the actual concentration of these antioxidants in colonic mucosa. It is also not known whether a relationship exists between serum and mucosal tissue antioxidant levels. Previous studies evaluating the occurrence of polyps after supplementation with vitamin E and beta-carotene have yielded mixed results. The aim of this study was to determine the concentrations of seven micronutrient antioxidants (alpha- and gamma-tocopherol, lutein, beta-cryptoxanthin, lycopene, and alpha- and beta-carotene) in colonic mucosa and to determine whether serum levels of each antioxidant could predict levels of that antioxidant in the right and left colon of patients with normal mucosa or in those with adenomatous polyps.

**METHODS:** Mucosal tissue concentrations and serum levels of antioxidants were determined in 10 patients with adenomatous polyps and 15 control subjects (GI patients with normal colonic mucosa). Mucosal tissue samples were obtained from both the right and left colon in all patients. **RESULTS:** Patients with polyps similar serum antioxidant status similar to that of control. However, polyp patients had significantly lower concentrations of all seven antioxidants in both the right ( $p < 0.0070$ ) and left colon ( $p < 0.0026$ ) than did controls. Finally, serum antioxidant levels predict right and left colon antioxidant levels in controls but not in patients with polyps. **CONCLUSIONS:** Patients with adenomatous polyps have low levels of micronutrient antioxidants in their colon mucosa. Because the serum levels of these antioxidants were similar in controls and polyp patients, our findings suggest an increased level of free radical activity in patients with polyps compared to normal subjects.

**Resveratrol inhibits human breast cancer cell growth and may mitigate the effect of linoleic acid, a potent breast cancer cell stimulator.**

Nakagawa H, Kiyozuka Y, Uemura Y, Senzaki H, Shikata N, Hioki K, Tsubura A. Department of Pathology II, Kansai Medical

Resveratrol is a naturally occurring product found in grapes and wine. The effect of synthetic Resveratrol on the growth of estrogen receptor (ER)-positive (KPL-1 and MCF-7) and -negative (MKL-F) human breast cancer cell lines was examined. Resveratrol at low concentrations caused cell proliferation in ER-positive lines (KPL-1,  $< \text{or} = 22 \text{ microM}$ ; MCF-7,  $< \text{or} = 4 \text{ microM}$ ) whereas at high concentrations ( $> \text{or} = 44 \text{ microM}$ ) it caused suppression of cell growth in all three cell lines examined. Growth suppression was due to apoptosis as seen by the appearance of a sub-G1 fraction. The apoptosis cascade up-regulated Bax and Bak protein, down-regulated Bcl-xL protein, and activated caspase-3. Resveratrol (52-74  $\text{microM}$ ) antagonized the effect of linoleic acid, a potent breast cancer cell stimulator, and suppressed the growth of both ER-positive and -negative cell lines. Thus, Resveratrol could be a promising anticancer agent for both hormone-dependent and hormone-independent breast cancers, and may mitigate the growth stimulatory effect of linoleic acid in the Western-style diet.

### **Colon cancer prevention with a small amount of dietary perilla oil high in alpha-linolenic acid in an animal model.**

Narisawa T, Fukaura Y, Yazawa K, Ishikawa C, Isoda Y, Nishizawa Y. Akita University College of Allied Medical Science, Japan.

**BACKGROUND.** Epidemiologic and experimental studies suggest that dietary fish oil and vegetable oil high in omega-3 polyunsaturated fatty acids (PUFAs) suppress the risk of colon cancer. The optimal amount to prevent colon carcinogenesis with perilla oil high in omega-3 PUFA alpha-linolenic acid in a 12% medium-fat diet was investigated in female F344 rats. For comparison, safflower oil high in omega-6 PUFA linoleic acid was used. **METHODS.** Thirty or 25 rats at 7 weeks of age in each group received an intrarectal dose of 2 mg N-methyl-N-nitrosourea 3 times weekly in weeks 1 and 2 and were fed the diets with various levels of perilla oil and safflower oil throughout the experiment. **RESULTS.** The incidence of colon cancer at the termination of the experiment at week 35 was 40%, 48% and 32% in the rats fed the diets with 3% perilla oil plus 9% safflower oil, 6% perilla oil plus 6% safflower oil, and 12% perilla oil plus 0% safflower oil, respectively, whereas it was 67% in the rats fed the control diet with 0% perilla oil plus 12% safflower oil. The amount of diet consumed and the body weight gain were identical in all of the dietary groups. The ratios of omega-3 PUFA to omega-6 PUFA in the serum and the colonic mucosa at week 35 were increased in parallel to the increased intake of perilla oil. **CONCLUSIONS.** The results suggest that a relatively small fraction of perilla oil, 25% of total dietary fat, may provide an appreciable beneficial effect in lowering the risk of colon cancer.

**Soy and Cancer** Natural Medicine News. 2000 Jan-Feb, p. 8. Long Island City, NY

### **Role of cytokines in cancer cachexia in a murine model of intracerebral injection of human tumours.**

Negri DR, Mezzanzanica D, Sacco S, Gadina M, Benigni F, Cajola L, Finocchiaro G, Ghezzi P, Canevari S. Unit of Molecular Therapies, Department of Experimental Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, Milano, 20133, Italy.

To study the role of cytokines that are relevant in cancer cachexia syndrome due to intracerebral tumours, mice were injected with human A431 epidermoid carcinoma, OVCAR3 ovarian carcinoma and GBLF glioma cells comparing intracerebral (i.c.) and systemic (i.p. or s.c.) routes of implantation. Anorexia and weight loss developed within 7-10 days in mice injected i.c. with A431 or OVCAR3 cells well before a large tumour developed, while i.c.-injected GBLF cells did not induce cachexia until day 20, when the tumour was large. By contrast, mice injected i.p. or s.c. developed tumours without evidence of anorexia. Thus, intracerebrally-growing A431 and OVCAR3 resulted in cancer cachexia independent of tumour mass, and we investigated their cytokine pattern. Serum levels of murine and human cytokines are not predictive of cancer cachexia development. Reverse-transcriptase polymerase chain reaction (RT-PCR) analysis revealed in the brain of i.c.-injected A431 tumour-bearing mice expression of human interleukin-(IL-)1alpha, IL-1beta and LIF in all samples and IL-6 in two of four samples while in i.c.-injected OVCAR3 tumour-bearing animals IL-6, and LIF were detected in all samples and tumour necrosis factor-alpha (TNFalpha) in two of four samples. Only LIF was expressed in brains of mice injected with GBLF cells. Murine IL-6 was increased only in the brains of A431-bearing mice. Only mice injected i.c. simultaneously with a monoclonal antibody (mAb) directed against the murine IL-6 receptor and OVCAR3 cells, but not those with mAb and A431 cells, showed a significant increase in survival time with a partial and temporary attenuation of cachexia symptoms. These results suggest that IL-6 in OVCAR3 model may be important cachectogenic factor when centrally released by even a limited number of tumour cells. Copyright 2001 Academic Press.

### **Melatonin as biological response modifier in cancer patients.**

Anticancer Res 1998 Mar-Apr;18(2B):1329-32

The neuroendocrine system modulates the immune response through neuropeptides and neurohormones, findings which point to the existence of a neuro-endocrine-immune system regulatory axis. At the same time, there is growing evidence that the pineal gland has anti-neoplastic properties, which include the action of its principal hormone, melatonin (MLT), on the immune system through the release of cytokines by activated T-cells and monocytes. The present study was carried out on 31 patients (19 males and 12 females, age range 46-73 years) with advanced solid tumors (7 gastric, 9 enteric, 8 renal, 5 bladder, 2 prostate) who either failed to respond to chemotherapy and radiotherapy or showed insignificant responses and were therefore shifted to MLT therapy (10 mg/die orally for 3 months). We obtained blood samples just before the start of MLT administration and after 30 days of therapy. Plasma was collected in EDTA tubes on ice, immediately centrifuged at 4 degrees C and stored frozen at -80 degrees C; samples were measured by immunoradiometric assays (Medgenix-Fleurus, Belgium) for tumor necrosis factor alpha (TNF), interleukin-1, 2 and 6 (IL-1, IL-2, IL-6) and interferon gamma (IFN). We used Student's paired t-test to compare each patient's cytokine circulating levels before and after MLT administration and found a significant differences ( $p < 0.05$ ). After 3 months of therapy, none of our patients displayed adverse reactions to MLT or had to discontinue treatment. Nineteen patients (61%) showed disease progression. The other 12 (39%), however, achieved disease stabilization with no further growth of either the primary tumor or of secondaries; moreover, they experienced an improvement in their general well-being, in terms of Tchekmedyan's criteria, associated with a significant decrease of IL-6 circulating levels. These findings are consistent with the hypothesis that MLT modulates immune function in cancer patients by activating the cytokine system which exerts growth-inhibitory properties over a wide range of tumor cell types. Furthermore, by stimulating the cytotoxic activity of macrophages and monocytes, MLT plays a critical role in host defence against the progression of neoplasia.

### **Alpha-tocopheryl succinate epitomizes a compound with a shift in biological activity due to pro-vitamin-to-vitamin conversion.**

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With the advent of the third millennium, a number of pathologies have been eradicated or taken under control. However, the incidences, of cancer and atherosclerosis, the two most common causes of death in developed countries, have increased or, in some instances, only stagnated. Therefore there has been an intensive search for agents effective against such life-threatening conditions. Accordingly, the potential anti-atherogenic activity of vitamin E analogs has been studied extensively. Interestingly, recent reports strongly suggest that certain vitamin E analogs, represented in particular by alpha-tocopheryl succinate (alpha-TOS), also possess anti-neoplastic activity. In this communication, we review our current understanding of the molecular basis for these double effects of alpha-TOS and propose a testable hypothesis, according to which this semi-synthetic analog exerts both anti-atherogenic and anti-neoplastic activities. We propose that the prevalence of each activity depends on the actual form of the vitamin E analog. That is, the conversion of the pro-vitamin E form, alpha-TOS, to the corresponding vitamin form, alpha-tocopherol, makes this anti-neoplastic agent active against inflammatory diseases like atherosclerosis.

### **Carcinogenicity of lipid-lowering drugs.**

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JAMA 1996 Jan 3; 2275: 55-60.

**OBJECTIVE**--To review the findings and implications of studies of rodent carcinogenicity of lipid-lowering drugs. **DATA SOURCES**--Summaries of carcinogenicity studies published in the 1992 and 1994 Physicians' Desk Reference (PDR), additional information obtained from the US Food and Drug Administration, and published articles identified by computer searching, bibliographies, and consultation with experts. **STUDY SAMPLE**--We tabulated rodent carcinogenicity data from the 1994 PDR for all drugs listed as "hypolipidemics." For comparison, we selected a stratified random sample of antihypertensive drugs. We also reviewed methods and interpretation of carcinogenicity studies in rodents and results of clinical trials in humans. **DATA SYNTHESIS**--All members of the two most popular classes of lipid-lowering drugs (the fibrates and the statins) cause cancer in rodents, in some cases at levels of animal exposure close to those prescribed to humans. In contrast, few of the antihypertensive drugs have been found to be carcinogenic in rodents. Evidence of carcinogenicity of lipid-lowering drugs from clinical trials in humans is inconclusive because of inconsistent results and insufficient duration of follow-up. **CONCLUSIONS**--Extrapolation of this evidence of carcinogenesis from rodents to humans is an uncertain process. Longer-term clinical trials and careful postmarketing surveillance during the next several decades are needed to determine whether cholesterol-lowering drugs cause cancer in humans. In the meantime, the results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be

avoided except in patients at high short-term risk of coronary heart disease.

**Beyond Aspirin 2000.** Newmark, T. et al. Prescott, AZ: Hohm Press.

**Austrian Researchers Find that Enzymes Restrict Out-of-Control Growth Factor Tied to Women's Breast Cancer 2000**  
NewsEdge. (<http://www.wobenzymonline.com/cancer03.html>).

**Cell growth inhibition by a novel vitamin K is associated with induction of protein tyrosine phosphorylation.**

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J Biol Chem 1998 Apr 17;273(16):9906-11

We have shown that a synthetic vitamin K analog, 2-(2-mercaptoethanol)-3-methyl-1,4-naphthoquinone or compound 5 (Cpd 5), potently inhibits cell growth and suggested that the analog exerts its effects mainly via sulfhydryl arylation rather than redox cycling. Since protein-tyrosine phosphatases (PTPases), which have pivotal roles in many cellular functions, have a critical cysteine in their active site, we have proposed PTPases as likely targets for Cpd 5. To test this hypothesis, we examined the effects of Cpd 5 on protein tyrosine phosphorylation of cellular proteins and on the activity of PTPases. We found that Cpd 5 rapidly induced protein tyrosine phosphorylation in a human hepatocellular carcinoma cell line (Hep3B) at growth inhibitory doses, and the effect was blocked by thiols but not by non-thiol antioxidants or tyrosine kinase inhibitors. Cpd 5 inhibited PTPase activity, which was also significantly antagonized by reduced glutathione. Furthermore, the well studied PTPase inhibitor orthovanadate also induced protein tyrosine phosphorylation and growth inhibition in Hep3B cells. These results suggest that inhibition of cellular PTPases by sulfhydryl arylation and subsequent perturbation of protein tyrosine phosphorylation may be involved in the mechanisms of Cpd 5-induced cell growth inhibition.

**Thromboxane A(2) regulation of endothelial cell migration, angiogenesis, and tumor metastasis.**

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Prostaglandin endoperoxide H synthases and their arachidonate products have been implicated in modulating angiogenesis during tumor growth and chronic inflammation. Here we report the involvement of thromboxane A(2), a downstream metabolite of prostaglandin H synthase, in angiogenesis. A TXA(2) mimetic, U46619, stimulated endothelial cell migration. Angiogenic basic fibroblast growth factor (bFGF) or vascular endothelial growth factor (VEGF) increased TXA(2) synthesis in endothelial cells three- to fivefold. Inhibition of TXA(2) synthesis with furegrelate or CI reduced HUVEC migration stimulated by VEGF or bFGF. A TXA(2) receptor antagonist, SQ29,548, inhibited VEGF- or bFGF-stimulated endothelial cell migration. In vivo, CI inhibited bFGF-induced angiogenesis. Finally, development of lung metastasis in C57Bl/6J mice intravenously injected with Lewis lung carcinoma or B16a cells was significantly inhibited by thromboxane synthase inhibitors, CI or furegrelate sodium. Our data demonstrate the involvement of TXA(2) in angiogenesis and development of tumor metastasis. Copyright 2000 Academic Press.

**Antitumor-promoting activity of allixin, a stress compound produced by garlic**

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Cancer Journal ( CANCER J. ) ( France ) 1990 , 3/1 (20-21)

Since a protective effect of garlic on human cancer, as well as on experimental animal tumors, has been reported, it is worthwhile surveying anti-carcinogenic principles in garlic. In this study, we proved the antitumor-promoting activity of allixin, which was recently identified as a stress compound produced by garlic. Firstly, allixin was found to be promising in the in vitro test of screening for antitumor-promoter activity; allixin inhibited the enhanced phospholipid metabolism of cultured cells induced by a tumor promotor, 2-O-tetradecanoylphorbol-13-acetate (TPA). Furthermore, allixin was proved to suppress the promoting process of two-stage carcinogenesis in vivo; allixin suppressed the promoting activity of TPA on skin tumor formation in 7,12-dimethylbenz(a)anthracene-initiated mice. Since allixin seems to have no side effects, it may be useful for prevention of human cancer.

**Development of a radiochemical cyclooxygenase-1 and -2 in vitro assay for identification of natural products as inhibitors of prostaglandin biosynthesis.**

J Nat Prod 1998 Jan;61(1):2-7

A radiochemical enzyme assay for studying cyclooxygenase (COX)-catalyzed prostaglandin biosynthesis in vitro was optimized with respect to both COX-1 and COX-2 activity. The assay can be used to assess the relative selectivity of plant-derived inhibitors on COX-1 and COX-2. Assay conditions were optimized for both enzymes with respect to concentration of cofactors (l-epinephrine, reduced glutathione, and hematin), activation time (enzyme and cofactors), reaction time, and pH. Moreover, the kinetic parameters,  $K_m$  and  $K_{cat}$ , of both enzymes were estimated. Five COX inhibitors were used to validate the assay, indomethacin, aspirin, naproxen, ibuprofen, and the arylsulfonamide NS-398, all with different COX selectivity and time dependency. Time-dependent inhibition was determined by comparing the inhibition, with and without preincubation of enzyme and inhibitor. Two flavonoids, (+)-catechin and quercitrin, were examined with respect to inhibition of COX-catalyzed prostaglandin biosynthesis. (+)-Catechin showed equal inhibitory effects on the two enzymes. Quercitrin was found to be inactive toward both COX-1- and COX-2-catalyzed prostaglandin biosynthesis. The optimization procedure resulted in a considerable reduction of the amount of enzyme required for adequate prostaglandin biosynthesis and a reliable method suited to evaluate natural products on inhibition of COX-2-catalyzed prostaglandin biosynthesis, as well as on COX-1.

**Vitamin D Is for Cancer Defense** Nutrition Science News. 2000 Mar  
([http://exchange.healthwell.com/nutritionsciencenews/nsn\\_Backs/Mar\\_00vitamind.cfm](http://exchange.healthwell.com/nutritionsciencenews/nsn_Backs/Mar_00vitamind.cfm)).

**Effect of fish oil, arginine, and doxorubicin chemotherapy on remission and survival time for dogs with lymphoma: a double-blind, randomized placebo-controlled study.**

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Cancer 2000 Apr 15;88(8):1916-28

**BACKGROUND:** Polyunsaturated n-3 fatty acids have been shown to inhibit the growth and metastasis of tumors. This double-blind, randomized study was designed to evaluate the hypothesis that polyunsaturated n-3 fatty acids can improve metabolic parameters, decrease chemical indices of inflammation, enhance quality of life, and extend disease free interval and survival time for dogs treated for lymphoblastic lymphoma with doxorubicin chemotherapy. **METHODS:** Thirty-two dogs with lymphoma were randomized to receive one of two diets supplemented with menhaden fish oil and arginine (experimental diet) or an otherwise identical diet supplemented with soybean oil (control diet). Diets were fed before and after remission was attained with up to five dosages of doxorubicin. Parameters examined included blood concentrations of glucose, lactic acid, and insulin in response to glucose and diet tolerance tests; alpha-1 acid glycoprotein; tumor necrosis factor; interleukin-6; body weight; amino acid profiles; resting energy expenditure; disease free interval (DFI); survival time (ST); and clinical performance scores. **RESULTS:** Dogs fed the experimental diet had significantly ( $P < 0.05$ ) higher mean serum levels of the n-3 fatty acids docosahexaenoic acid (C22:6) and eicosapentaenoic acid (C20:5) compared with controls. Higher serum levels of C22:6 and C20:5 were associated with lesser ( $P < 0.05$ ) plasma lactic acid responses to intravenous glucose and diet tolerance testing. Increasing C22:6 levels were significantly ( $P < 0.05$ ) associated with longer DFI and ST for dogs with Stage III lymphoma fed the experimental diet. **CONCLUSIONS:** Fatty acids of the n-3 series normalize elevated blood lactic acid in a dose-dependent manner, resulting in an increase in DFI and ST for dogs with lymphoma. Copyright 2000 American Cancer Society.

**All-trans retinoic acid modulates Fas antigen expression and affects cell proliferation and apoptosis in combination with anti-Fas monoclonal antibody in the human myeloma cell line, U266B1.**

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Exp Hematol 1998 Jun;26(6):501-6

All-trans retinoic acid (ATRA) is a vitamin A derivative that induces the differentiation of myeloid leukemia cells in vitro and in vivo. Several investigators have recently reported that ATRA downregulates the production of interleukin-6 (IL-6) and the expression of IL-6 receptor (IL-6R) and also inhibits the proliferation of myeloma cells. It has also been reported that myeloma cells express Fas antigen, and in some of these cells apoptosis was induced by treatment with anti-Fas monoclonal antibody (mAb). In the present study, we demonstrated that ATRA increased Fas expression in the human myeloma cell line, U266B1. We observed that both apoptosis induction and growth inhibition were enhanced in cells exposed to a combination of anti-Fas mAb and ATRA compared with cells exposed to either treatment alone. We also examined whether ATRA modulated bcl-2, an anti-apoptosis protein, in U266B1 cells. Flow cytometry analysis revealed that the mean fluorescence intensity of bcl-2 protein was slightly decreased in cells treated with ATRA. These results indicate that in U266B1 cells, combined treatment with anti-Fas mAb and ATRA enhances

the induction of apoptosis by modulating the expression of Fas and bcl-2 by ATRA.

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