Vitamin C and the Treatment of Cancer: Part II Abstracts and Commentary from the Scientific Literature

by Gary Null, PhD; Howard Robins, DPM; Mark Tanenbaum, DPM; and Patrick Jennings, Editor

This study found that ascorbic administered in drinking water (0.3%) inhibited the promoting effect of estradiol dipropionate on the 1,2-dimethylhydrazine-induced uterine sarcogenesis in CBA mice.

– L.S. Trukhanova, [Modifying Effect of Ascorbic Acid and Sodium Ascorbate on Uterine Carcomogenesis Induced by 1,2-dimethylhydrazine in CBA Mice], *Eksp Onkol,* 10(5), 1988, p. 65-66.

This study found that ascorbic acid intake affects in vivo N-ethyl-N-nitrosourea (ENU) mutagenicity in rats. The authors suggest that previously reported antioxidant inhibitory effects on carcinogenesis could be partially mediated by its effects on mutagenesis.

– A. Aidoo, et al., Ascorbic Acid (Vitamin C) Modulates the Mutagenic Effects Produced by an Alkylating Agent in Vivo, *Environ Mol Mutagen,* 24(3), 1994, p. 220-228.

This case-control, population-based study found Vitamin C intake, attenuated by age, level of education, and lifetime cigarette use, offers protective effects against developing cervical cancer.

– M.L. Slattery, et al., Dietary Vitamins A, C, and E and Selenium as Risk Factors for Cervical Cancer, *Epidemiology,* 1(1), January 1990, p. 8-15.

This paper reports the discovery of a new malignant human T-cell line – labeled PFI-285 in a boy with malignant lymphoma. One of the striking characteristics of this new T-cell line was its sensitivity to ascorbic acid, evidenced by the fact that concentrations as low as 50 mumuol/l resulted in cell death within hours.

– J. Helgestad, et al., Characterization of a New Malignant Human T-cell Line (PFI-285) Sensitive to Ascorbic Acid, *European Journal of Haematology,* 44(1), January 1990, p. 9-17.

This study found that oral administration of vitamin C can retard the onset of N-nitrosodiethylamine-induced liver cancer in rats.

– H. Kessler, et al., Potential Protective Effect of Vitamin C on Carcinogenesis Caused by Nitrosamine in Drinking Water: An Experimental Study on Wistar Rats, *European Journal of Surgery and Oncology,* 18(3), June 1992, p. 275-281.

The survival rate of mice bearing P388 leukemia and Ehrlich carcinoma was increased after treatment with a mixture of vitamins C and B12. All the mice receiving the vitamins outlived the control group. At the termination of the experiment 30 days later, 50% of the treated mice appeared normal and healthy, whereas the remainder showed signs of tumor distention.

– M.E. Poydock, et al., Influence of Vitamins C and B12 on the Survival Rate of Mice Bearing Ascites Tumor, *Exp Cell Biol,* 50(2), 1982, p. 88-91.

This study found that a daily dose of 50 mg/kg of vitamin C in combination with methylcholanthrene (MCA) over 9 months significantly reduced MCA-induced squamous cell carcinomas in mice and basal cell carcinomas in rats over a period of nine months. The authors conclude that vitamin C's antineoplastic effects are the result of increasing autophagic and cytolytic activity, increased collagen synthesis, and cell membrane disruption.

– A. Lupulescu, Ultrastructure and Cell Surface Studies of Cancer Cells Following Vitamin C Administration, *Exp Toxicol Pathol,* 44(1), March 1992, p. 3-9.

This study found that vitamin C reduced the incidence of DMBA-induced epithelial tumor in the hamster cheek pouch.

– P.D. Potdar, et al., Modulation by Vitamin C of Tumor Incidence and Inhibition in Oral Carcinogenesis, *Funct Dev Morphol,* 2(3), 1992, p. 167-172.

Previous studies have found that nitrosation can be decreased by the administration of ascorbic acid in vivo and that vitamin C-rich foods are inversely related to gastric cancer. This study treated 62 high risk patients for gastric cancer with 1g of ascorbic acid taken 4 times a day for four weeks. Results found that ascorbic acid given in high doses can reduce the intragastric formation of nitrite and N-nitroso compounds.

– P.I. Reed, et al., Effect of Ascorbic Acid on the Intragastric Environment in Patients at Increased Risk of Developing Gastric Cancer, *IARC Sci Publ,*(105), 1991, p. 139-142.

1000 mg/kg of ascorbic acid in combination with mitomycin and 5-fluorouracil significantly inhibited tumor growth in mice implanted with Lewis lung carcinoma cells relative to mice treated with mitomycin and 5-fluorouracil in the absence of ascorbic acid or animal that received only ascorbic acid alone.

– K. Nakano, et al., Antitumor Activity of Ascorbic Acid in Combination with Antitumor Agents Against Lewis Lung Carcinoma, *In Vivo,* 2(3-4), May-August 1988, p. 247-252.

This study found that 1 or 5g/liter of ascorbic acid in the drinking water significantly inhibited the growth of human mammary tumor fragments implanted beneath the renal capsule of immunocompetent mice. Mice fed a diet including 50g/kg ascorbic acid and 18 or 90 mg/liter of cupric sulfate in the drinking water also experienced inhibited tumor growth. The authors conclude ascorbic acid contains specific oxidation and degradation products that serve as antineoplastic agents for human mammary carcinoma.

– C.S. Tsao, et al., In Vivo Antineoplastic Activity of Ascorbic Acid for Human Mammary Tumor, *In Vivo,* 2(2), March-April 1988, p. 147-150.

This study found that administration of 500 mg/kg of L-ascorbic acid to athymic nude mice bearing human mammary carcinoma inhibited tumor cell growth. Treatment with L-ascorbic acid was also found to induce cellular DNA strand breaks and DNA crosslinks. When L-ascorbic acid was removed from cell cultures, researchers witnessed an immediate onset of spontaneous repair of single or double stranded DNA breaks. Reintroduction of L-ascorbic acid reversed this process.

– K. Pavelic, et al., Antimetabolic Activity of L-ascorbic Acid in Human and Animal tumors *International Journal of Biochemistry,* 21(8), 1989, p. 931-935.

This population-based dietary study found inverse relationship between vitamin C consumption in women and the risk of developing cancer in the lower urinary tract.

– A.M. Nomura, et al., Dietary Factors in Cancer of the Lower Urinary Tract, *International Journal of Cancer,* 48(2), May 10, 1991, p. 199-205.

An inverse relationship was found in this population-based case-control study between the intake of vitamin C and invasive cervical cancer.

– R. Verreault, et al., A Case-Control Study of Diet and Invasive Cervical Cancer, *International Journal of Cancer,* 43(6), June 15, 1989, p. 1050-1054.

This study found that guinea pigs fed high vitamin C diets experienced a significantly less mutagenic effect after being injected with K2Cr207 than those fed a vitamin C-deficient diet. Vitamin C-deficient animals also suffered greater mutagenic and toxic effects from hexavalent chromium. High vitamin C-guinea pigs experienced no mutagenic effects in the bone marrow or changes in microsomal enzymes in the liver following exposure to bichromate. In interpreting their results, the authors suggest that vitamin C's protective effects likely consist in the enhanced extracellular and intracellular reduction of hexavalent chromium in the less toxic and less mutagenic trivalent chromium.

– E. Ginter, et al., Vitamin C Lowers Mutagenic and Toxic Effect of Hexavalent Chromium in Guinea Pigs, *International Journal of Vitamin and Nutritional Research,* 59(2), 1989, p. 161-166.

In this study, ascorbic acid deficiencies in guinea pig were found to change leukocyte morphology and significantly interfere with the bactericidal effectiveness of circulating leukocytes against ingested, cell-associated, and extracellular bacterial cells of Actinomyces viscosus. Adding vitamin C can reverse this activity.

– M.C. Goldschmidt, et al., The Effect of Ascorbic Acid Deficiency on Leukocyte Phagocytosis and Killing of Actinomyces Viscosus, *International Journal of Vitamin and Nutrition Research,* 58(3), 1988, p. 326-334.

This review article points out the importance of vitamin C, as well as vitamins A and E, as regulators of cancer cell differentiation, cell regression, membrane biogenesis, DNA, RNA, protein, and collagen synthesis, as well as transformation of precancer cells into cancer cells. Vitamins C, A, and E can reverse the cancer cell to the normal phenotype and possess cytotoxic and cytostatic effects.

– A. Lupulescu, The Role of Vitamins A, Beta-carotene, E and C in Cancer Cell Biology, *International Journal of Vitamin and Nutrition Research,* 64((1), 1994, p. 3-14.

This study found that mice consuming distilled water suffered from tumor growth after being injected with Ehrlich ascites tumor cells at a rate significantly faster than those consuming 0.1% ascorbic acid in distilled water.

– F.A. Tewfik, et al., The Influence of Ascorbic Acid on the Growth of Solid Tumors in Mice and on Tumor Control by X-Irradiation, *International Journal of Vitamin and Nutrition Research Suppl.,*23, 1982, p. 257-263.

This comprehenesive reivew article cites numerous studies supporting ascorbic acid's protective effects against cancer and recommends that it be used in treatment. Clinical trials over the last ten years are summarized, with the majority of them supporting this view. The authors predict that supplemental ascorbate will soon secure an established place in all full-scale therapeutic programs for cancer.

– E. Cameron, Vitamin C and Cancer: An Overview, *International Journal of Vitamin and Nutrition Research Suppl.,* 23, 1982, p. 115-127.

This study reported on two sets of Japanese clinical trials involving the use of supplemental ascorbate to treat terminal cancer patients. The first trial found average survival time of high ascorbate patients was 246 compared to 43 days for low ascorbate patients. Results of the second trial were similar, with high ascorbate patients surviving an average of 115 days compared to 48 days for those in the low ascorbate group.

– A. Murata, et al., Prolongation of Survival Times of Terminal Cancer Patients by Administration of Large Doses of Ascorbate,*International Journal of Vitamin and Nutrition Research Suppl.,* 23, 1982, p. 103-113.

This study demonstrated the effectiveness of ascorbic acid as a blocking agent in vivo and in vitro to N-Nitroso compounds, which can lead to cancer of the stomach.

– S.R. Tannenbaum, Preventive Action of Vitamin C on Nitrosamine Formation, *International Journal of Vitamin and Nutrition Research Suppl.,* 30, 1989, p. 109-113.

Ascorbic acid and dehydroascorbic acid have both been shown to favor ATP C+ cell multiplication in vitro at low doses and inhibit it at high doses. Ascorbic acid was found to be more effective in determining both sets of effects than dehydroascorbic acid. Fractioned rather than single administration of both substances proved to the most efficient method for inhibiting cell multiplication.

– F.S. Liotti, et al., Effects of Ascorbic and Dehydroascorbic Acid on the Multiplication of Tumor Ascites Cells in Vitro, *Journal of Cancer Research and Clinical Oncology,* 108(2), 1984, p. 230-232.

In this study, the oral administration of 525 mg/day of vitamin C greatly inhibited benzo(a)pyrene-induced local malignant tumors in rats relative to controls.

– G. Kallistratos and E. Fasske, Inhibition of Benzo(a)pyrene Carcinogenesis in Rats with Vitamin C, *Journal of Cancer Research and Clinical Oncology,* 97(1), 1980, p. 91-96.

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This study found that catecholamine-positive neuroblastoma cell line SK-N-SH was inhibited by high doses of ascorbic acid as were LS cells and catecholamine-negative SK-N-LO, albeit to a smaller extent.

– S.L. Baader, et al., Ascorbic-acid-mediated Iron Release from Cellular Ferritin and its Relation to the Formation of DNA Strand Breaks in Neuroblastoma Cells, *Journal of Cancer Research and Clinical Oncology,* 120(7), 1994, p. 415-421.

This study examined the effects of vitamin C on the efficacy and adverse effects of drug 864T in Ehrlich ascites carcinoma (EAC) cells in vivo. Results demonstrated that vitamin C both potentiates the anticancer effect of 864T as well as helps to counteract the drug's adverse effects.

– M.M. el-Merzabani MM, et al., Potentiation of therapeutic Effect of Methanesulphonate and Protection Against its Organ Cytotoxicity by Vitamin C in Ehrlich Ascites Carcinoma Bearing Mice, *Journal of Pharm Belg,* 44(2), March-April 1989, p. 109-116.

This study documents the case of one patient given large doses of ascorbic acid with indomethacin who consequently experienced a slow tumor resolution that has continued for 14 months. Similar effects were seen in a second patient receiving the same treatment.

– W.R. Waddell and R.E. Gerner, Indomethacin and Ascorbate Inhibit Desmoid Tumors, *Journal of Surg Oncol,* 15(1), 1980, p. 85-90.

This comparative study of normal and malignant conditions in humans and in mice found that serum levels of vitamin C were lower in all human malignant cases relative to controls. With respect to mice, results showed that vitamin C and vitamin A supplementation administered at the start of tumor development reduced both tumor take and rate of growth and prolonged host survival relative to controls.

– J. Ghosh and S. Das, Evaluation of Vitamin A and C Status in Normal and Malignant Conditions and Their Possible Role in Cancer Prevention, *Japanese Journal of Cancer Research,* 76(12), December 1995, p. 1174-1178.

This study compared 294 incurable patients treated with supplemental ascorbate with 1,532 untreated patients who served as controls over a 4.5 year period. The median survival time of the ascorbate group was 343 days compared to 180 days for the controls.

– E. Cameron and A. Campbell, Innovation vs. Quality Control: An 'Unpublishable' Clinical Trial on Supplemental Ascorbate in Incurable Cancer, *Medical Hypotheses,* 36(3), November 1991, p. 185-189.

Noting that previous studies have found ascorbic acid and its salts to be toxic to tumor cells in vitro and in vivo, this study presents data showing that ascorbic acid plasma levels can be sustained above levels toxic to tumor cells in vitro. The authors argue that ascorbic acid's cytotoxic properties should qualify it for consideration as a chemotherapeutic agent.

– N.H. Riordan, et al., Intravenous Ascorbate as a Tumor Cytotoxic Chemotherapeutic Agent, *Medical Hypotheses,* 44(3), March 1995, p. 207-213.

This article examined the results and methodology of a controversial case-control study involving the treatment of 100 incurable patients with 10g a day of vitamin C. The study has received criticism for not being conducted on a randomized, double-blind basis (out of ethical considerations). Instead, test cases were studied against historical controls. Results found that patients receiving vitamin C outlived controls by an average of 255 days (671%). This author considers the various criticisms the study has received, yet concludes that vitamin C is likely to have increased survival time an average of 100% in cancer patients who had failed to respond to previous treatments.

– M. Jaffey, Vitamin C and Cancer: Examination of the Value of Leven Trial Results Using Broad Inductive Reasoning, *Medical Hypotheses,* 8(1), 1982, p. 49-84.

This paper reports on the case of a 42 year-old man suffering from reticulum cell sarcoma who experienced two complete spontaneous regressions following the intravenous administration of high doses of ascorbate in 1975.

– A. Campbell, et al., Reticulum Cell Sarcoma: Two Complete Spontaneous Regressions, in Response to High-Dose Ascorbic Acid Therapy. A Report on Subsequent Progress, *Oncology* (1991) 48(6), 1991, p. 495-497.

This study looked at vitamin C's effects on methylcholanthrene-induced local malignant sarcomas in mice. Results found that doses of 6, 25 and 35 mg/day of vitamin C five times weekly for 20 weeks offered significant prevention against the induction of sarcomas relative to controls.

– M. Abdel-Galil, Preventive Effect of Vitamin C (L-ascorbic acid) on Methylcholanthrene-induced Soft Tissue Sarcomas in Mice, *Oncology,* 43(5), 1986, p. 335-337.

This 12-year mortality follow-up study reports that vitamin C is inversely associated with overall mortality from cancer and cadiovascular disease.

– M. Eichholzer, et al., Inverse Correlation Between Essential Antioxidants in Plasma and Subsequent Risk to Develop Cancer, Ischemic Heart Disease and Stroke Respectively: 12-Year Follow-up of the Prospective Basel Study, *EXS,* 62, 1992, p. 398-410.

This double-blind, randomized, crossover study found that ascorbic acid significantly reduced muscle soreness in subjects following strenuous use of posterior calf muscles relative to subjects taking a lactose placebo.

– M. Kaminski and R. Boal, An Effect of Ascorbic Acid on Delayed-onset Muscle Soreness, *Pain,* 50(3), September 1992, p. 317-321.

This review article cites immunological studies documenting ascorbic acid's ability to induce immunity in mice against certain types of cancer. The authors argue that ascorbate works as an effective thiolprive in oxygenated cancer tissues which is primarily responsible for its immunological effects.

– F.E. Knock, et al., Ascorbic Acid as a Thiolprive: Ability to Induce Immunity Against Some Cancers in Mice, *Physiol Chem Phys,* 13(4), 1981, p. 325-333.

This study found that combinations of vitamin C and cisplatin lead to the regression of Dalton's lymphoma tumor activity in mice, which resulted in significantly increased host survival.

– S.B. Prasad, et al., Use of Subtherapeutical Dose of Cisplatin and Vitamin C Against Murine Dalton's Lymphoma, *Pol J Pharmacol Pharm,* 44(4), July-August 1992, p. 383-391.

This study found that the administration of 8g/day over 8-10 days before starting chemotherapy with cytostatics decreased p-hydroxyphenyl lactic acid (pHPLA) excretion in leukemia patients. Mice given 5 mg, 2x/wk, sc, 5wk of pHPLA with 250 mg/100 ml of ascorbic acid were also found to experience a reduction in the incidences of hepatoma, leukemia and bladder cancer. Based on these results, the authors argue that pHPLA carcinogenesis is inhibited by ascorbic acid.

– M.O. Raushenbakh, et al., [Effect of Ascorbic Acid on Formation and Leukemogenic Activity of P-Hydroxyphenyllactic Acid], *Probl Gematol Pereliv Krovi,* 27(7), 1982, p.3-6.

This study showed that treatment with vitamin C and chlorophyllin significantly reduced cytotoxicity and the rate of 6-sulfooxymethyl benzo[a]pyrene (SMBP) induced mutagenicity in animal and bacterial cell cultures.

–A.S. Chung and Y.S. Cho, Antimutagenicity of Vitamin C and Chlorophyllin on 6-sulfooxymethyl benzo[a]pyrene in Salmonella Typhimurium and V79 Cell Line, *Proceedings of the Annual Meeting of the American Association of Cancer Researchers,* 36, 1995, A755.

Rat liver carcinogenesis was found to be inhibited by vitamin C and vitamin E derivatives in this study when administered at concentrations of 0.01, 0.05 or 0.10% for 12 weeks. Among the four vitamin derivatives administered, 2-O-octadecylascorbic acid (CV3611) proved to be the most effective.

–D. Nakae, et al., Inhibitory Effects of Vitamin C and E Derivatives on Rat Liver Carcinogenesis Induced by a Choline-Deficient L-Amino Acid (CDAA)-Defined Diet, *Proceedings of the Annual Meeting of the American Association of Cancer Researchers,* 34, 1993, A729.

In this study, Metha tumor cell proliferation was found to be inhibited in vitro after simultaneous exposure to diethyldithiocarbamate (DDC) (1 to approx 2x10(-7) and ascorbic acid (1 to approx 5x10(-5)M). The two substances were able to inhibit tumor proliferation at slightly lower doses when cells were pretreated at 37°C for one hour. In a mouse injected with 2 million tumor cells, 25 mg or 50 mg of ascorbic acid and 10 mg of DDC was also observed to inhibit tumor growth.

– H. Mashiba and K. Matsunaga, Inhibition of Metha Tumor Cell Proliferation in Vitro and Tumor Inhibiton of Metha Tumor Cell Proliferation in Vitro and Tumor Growth in Combined Use of Diethyldithiocarbamate with Ascorbic Acid, *Proceedings of the Annual Meeting of the American Association of Cancer Researchers,* 33, 1992, A2649.

This study of ultraviolet light-induced malignant skin tumors and other lesions in hairless mice found that animals fed a standard diet including L-ascorbic acid experienced significantly less malignant lesions as well as significant delays in those that did develop relevant to controls.

– W.B. Dunham, et al., Effects of Intake of L-ascorbic Acid on the Incidence of Dermal Neoplasms Induced in Mice by Ultraviolet Light, *Proceedings of the National Academy of Sciences,* 79(23), December 1982, p. 7532-7536.

This study found that vitamin C prevented cigarette smoke-induced leukocyte adhesion to micro and macrovascular endothelium and leukocyte-platelet aggregate formation in mice.

– H.A. Lehr, et al., Vitamin C Prevents Cigarette Smoke-Induced Leukocyte Aggregation and Adhesion to Endothelium in Vivo, *Proceedings of the National Academy of Sciences,* 91(16), August 2, 1994, p. 7688-7692.

Percentages of L-ascorbic acid contained in food ranging from 0.076% to 8.3% were studied for their effects on spontaneous mammary tumors in mice. Results showed that as ascorbic acid dosages were increased, significant decreases occurred in the first-order appearance tumors after lag time detection by palpation when compared to controls.

– L. Pauling, et al., Effect of Dietary Ascorbic Acid on the Incidence of Spontaneous Mammary Tumors in RIII Mice, *Proceedings of the National Academy of Sciences,* 82(15), August 1985, p. 5185-5189.

In this study, 6-deoxy-6-bromo-ascorbic acid (6-Br-AA) in concentrations 10(-1) to 10(-8)M and incubated for periods of 2, 18, 24 and 72 hours was found to greatly inhibit the growth and DNA synthesis of melanoma cells in mice and was confirmed by in vivo experiments. Mice given 9 mg of 6-Br-AA three times daily for 16 days experienced tumor-suppressing effects on solid melanoma.

– M. Osmak, et al., 6-Deoxy-6-bromo-ascorbic Acid Inhibits Growth of Mouse Melanoma Cells, *Res Exp Med* (Berl), 190(6), 1990, p. 443-449.

In this seven year follow-up study of 2,974 men, average vitamin C levels were found to be lower in stomach cancer death cases relative to controls.

– H.B. Stahelin, [Vitamins and Cancer: results of a Basel Study], *Soz Praventivmed,* 34(2), 1989, p. 75-77.

This study found that ascorbic acid incubation is cultured stomach cancer surgery specimens resulted in a 50-90% increase in the rate of 5-fluorouracil incorproation into RNA of 5-fluorouracil-sensitive stomach tumors and in an approximately 50% increase of the rate of 5-fluorouracil-resistant tumors.

– M.P. Shlemkevich, [Effect of Ascorbic Acid on In Vitro (6-3H)-5-Fluorouracil Incorporation into RNA of Stomach Cancer Tissue, Normal Gastric Mucosa, and Normal Small Intestine Mucosa], *Vopr Med Khim,* 29(1), 1983, p. 17-19.

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This study demonstrated that a 3% solution of ascorbic acid in drinking water added to estradiol propionate (carcinogen) decreased the incidence of uterine sarcoma tumors in mice by 35%.

– L.S. Trukhanova, et al., [The Inhibitory Effect of Ascorbic Acid on the Estrogen-Stimulated Promotion of Uterine Sarcoma Development in Mice] *Vopr Onkol,* 36(5), 1990, p. 563-567.

This study showed that injections of ascorbic acid before onset and at the start of tumor development decreased blood and urine 3-oxyanthranilic acid-antigen levels down to its eventual elimination from the body in rats and mice. Such activity was found to prevent the subsequent development of hepatoma.

– T.A. Korosteleva, et al., [Effects of the Administration of Ascorbic Acid on 3-OAA-antigen Levels Formed During Chemical Hepatocarcinogenesis], *Vopr Onkol,* 35(12), 1989, p. 1455-1461.

In this randomized study, postoperative treatment of 95 stomach cancer patients with vitamins C, E and A following, resulted in a decreased rate of postoperative complications from 30.9% to 1.9%.

– V.N. Sukolinskii and T.S. Morozkina, [Prevention of Postoperative Complications in Patients with Stomach Cancer Using an Antioxidant Complex], *Vopr Onkol,* 35(10), 1989, p. 1242-1245.

This study found that cancer patients suffered from a decreased level of ascorbic acid relative to non-cancer patients in addition to showing that such decreases correlated with an increase in blood concentrations of malonic and pyruvic acids. When cancer patients were given 1.5 g of ascorbic acid daily over a period of 7 days, blood levels of ascorbic acid returned to almost normal and lactate and pyruvate levels exhibited a decrease. In addition to these changes, ascorbic acid deficiencies were found to result in an increased risk of postoperative complications. This risk was decreased by increasing the levels of ascorbic acid in the blood of deficient patients.

– E.G. Gorozhanskaia, et al., [The Role of Ascorbic Acid in the Combined Preoperative Preparation of Cancer Patients], *Vopr Onkol,* 35(4), 1989, p. 436-441.

This study showed that mice treated with doses of 1.5, 0.25, and 0.025% of ascorbic acid in drinking water all experienced decreases in the frequency of N-nitroso compound induced tumors.

– N.L. Vlasenko, et al., [Effect of Different Doses of Ascorbic Acid on the Induction of Tumors with N-Nitroso Compound Precursors in Mice], *Vopr Onkol,* 34(7), 1988, p. 839-843.

Doses of 0.3, 0.75 or 1.5% of ascorbic acid administered in drinking water inhibited the growth of 1,2 dimethylhydrazine and estradiol-dipropionate induced uterine sarcomas in mice.

– L.S. Trukhanova, [Effect of Ascorbic Acid on the Induction of Uterine Sarcomas in Mice], *Vopr Onkol,* 33(11), 1987, p. 53-57.

The effect of high doses of ascorbic acid (100 mg/kg daily) on tyrosine metabolism and clinical course of acute lymphoblastic leukemia was studied in nine children. Ascorbic acid administration was shown to prevent or to considerably lower the excretion of a blastogenic metabolite of tyrosine – p-hydroxyphenylpyruvic acid. The treatment improved clinical blood count indexes, prevented hemorrhage and was followed by an earlier onset of complete remission after chemotherapy. Although chemotherapy suppressed p-hydroxyphenylpyruvic acid excretion, its level was inordinately high as late as on day 12. It is concluded that although the effects of ascorbic acid and cytostatic drugs on p-hydroxyphenylpyruvate hydroxylase level are similar, that of ascorbic acid is more specific and is followed by a complete recovery of tyrosine metabolism.

– V.N. Baikova, et al., [The Effect of Large Doses of Ascorbic Acid on Tyrosine Metabolism and Hemoblastosis Course in Children], *Vopr Onkol,* 28(9), 1982, p. 28-34.

This case-control study of diet and breast cancer in 2 Chinese populations found a strong inverse association between breast cancer and the intake of vitamin C, carotene, and crude fiber.

– J.M. Yuan, et al., Diet and Breast Cancer in Shanghai and Tianjin, China, *British Journal of Cancer,* 71, 1995, p. 1353-1358.

This review article looked at 12 case-control studies on the relationship between breast cancer and diet. The most consistently significant inverse association found was between vitamin C and breast cancer risk.

– G.R. Howe, et al., Dietary Factors and the Risk of Breast Cancer: Combined Analysis of 12 Case-Controlled Studies, *Journal of the National Cancer Institute,* 82, 1992, p. 561-569.

This review article cites results from several studies documenting the protective effects of vitamin C in reducing the risk of cervical cancer. One, in particular, found that women with the highest levels of dietary vitamin C decreased their chances of developing cervical cancer by 4-5 times compared to those with the lowest levels.

– J. VanEenwyk, The Role of Vitamins in the Development of Cervical Cancer, *The Nutrition Report,* 11(1), January 1993, p. 1-8.

Dietary vitamin C was found to be protective against cervical intraepithelial neoplasia in this case-control study.

– C.F. Amburgey, et al., Undernutrition as a Risk Factor for Cervical Intraepithelial Neoplasia: A Case-control Analysis, *Nutrition and Cancer,* 20(1), 1993, p. 51-60.

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