

## Cancer patients may very well tolerate the use of certain dietary supplements

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Cancer patients may very well tolerate the use of certain dietary supplements, with some specific benefits noted in the literature. A recent article published in *CA: A Cancer Journal for Physicians* (D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. *CA Cancer J Clin.* 2005 Sep-Oct;55(5):319-21. PMID: 16166076) stated that the use of “antioxidants might reduce the effects of conventional cytotoxic therapies”.

However, my own review of the literature shows that, in many cases, the use of antioxidants - and other nutritional supplements - have been determined to be compatible with conventional cancer therapies based on the published literature and that clinicians might better serve their patients if they adopt a more inquisitive approach as to whether or not specific supplements may play a role in aiding their conventional therapies. In some cases the supplements are deemed useful, but just not on the same day as the therapy. In others the supplements are highly recommended during and/or after the conventional therapies.

The article's overgeneralization has resulted in news headlines warning doctors and patients to avoid the use of all dietary supplements during cancer therapy. If true, a warning should also be issued for nutrient-rich foods like fruits, vegetables and nuts; especially if concentrated into juices. Since there is conflicting data and these nutrients are so essential, I do not support either warning. Physicians should research the documented use of nutrients that are compatible with the specific therapies that they are contemplating, which may result in better outcomes for their patients than the simple avoidance of nutrient-rich foods and dietary supplements that have already been shown to discourage cancer growth.

The large percentage of cancer patients that die of malnutrition has also been ignored in this article.<sup>9</sup> Improving the nutritional status of patients thus becomes almost as important as fighting the cancer, and in most cases the two are not contradictory.

Here is a breakdown of dietary supplements that are useful during therapy, broken down by classes of supplements. I have bolded some text for emphasis, with all direct quotes indicated by quotation marks:

### FISH OIL:

“The results of animal studies have demonstrated that the consumption of omega-3 fatty acids can slow the growth of cancer xenografts, **increase the efficacy of chemotherapy and reduce the side effects of the chemotherapy or of the cancer.** Molecular mechanisms postulated to contribute to the multiple benefits of omega-3 fatty acids include 1) suppressing the expression of cyclooxygenase-2 in tumors, thus decreasing proliferation of cancer cells and reducing angiogenesis in the tumor; 2) decreasing the expression of AP-1 and ras, two oncogenes implicated in tumor promotion; 3) inducing differentiation of cancer cells; 4) suppressing nuclear factor-kappaB activation and bcl-2 expression, thus allowing apoptosis of cancer cells; and 5) reducing cancer-induced cachexia. It seems reasonable to assume that after appropriate cancer therapy, consumption of omega-3 fatty acids might slow or stop the growth of metastatic cancer cells, increase longevity of cancer patients and improve their quality of life.”<sup>1</sup>

**Fish oil improved outcome in patients with solid tumors** and increases tumor necrosis factor production in malnourished cancer patients, prolonging survival.<sup>2</sup>

**Fish oil also improved outcomes in cancer treatments: wasting syndrome<sup>3</sup>, apoptosis of cancer cells (“in combination with standard treatments, supplementing the diet with (n-3) fatty acids may be a nontoxic means to improve cancer treatment outcomes and may slow or prevent recurrence of cancer.”)<sup>4</sup> (“We conclude that EPA inhibits the growth of HepG2 cells and mediates its effect, at least in part, via the Fas-mediated apoptosis. It appears that the effects of EPA on hepatoma cells are determined by the status of p53 and that wild-type p53 is a prerequisite for the anticancer effect of EPA.”)<sup>5,6</sup>, impairing tumor angiogenesis (“Review of the experimental data suggests that selective inhibitors of eicosanoid-synthesizing enzymes and dietary intervention with n-3 fatty acids merit clinical evaluation as adjuvant therapy and chemopreventive agents.”) while improving blood glucose<sup>7</sup>.**

## GLA:

Gamma linolenic acid with tamoxifen as primary therapy in breast cancer: **“T+GLA cases achieved a significantly faster clinical response** (objective response vs. static disease) than tamoxifen controls, evident by 6 weeks on treatment ( $p = 0.010$ ).”<sup>8</sup>

## VITAMINS/MALNUTRITION:

**Malnutrition actually kills about 40% of cancer patients!**<sup>9</sup> **Post-surgical lung cancer patients who take vitamin supplements are more likely to be long term survivors:** “Vitamin users had a longer median censored survival compared with nonusers (41 months versus 11 months;  $P = 0.002$ ).”<sup>10</sup>

A double blind clinical trial of biopsy-confirmed bladder cancer patients added either RDA-potency vitamins or megadose potency vitamins, plus zinc in RDA or megadose potency. “Overall recurrence was 24 of 30 patients (80%) in the RDA arm and 14 of 35 (40%) in the high dose arm ( $p = 0.0011$ , 2-tailed Fisher's exact test). Megadose vitamins A, B6, C and E plus zinc decrease bladder tumor recurrence in patients receiving BCG immunotherapy.”<sup>11</sup>

A trial of patients with malignant high-risk uveal (iris of the eye) melanoma (T3) were treated secondarily with biological dietary supplements after primary standard therapy, enucleation or brachytherapy. Secondary treatment consisted of natural amino-acids, trace minerals, folic acid and a diet containing neurogenic lipid fatty acid components. **It presented no side effects, no toxicity and was inexpensive. None of these patients has suffered recurrent disease.**<sup>12</sup>

**Metastatic breast cancer treatment is enhanced with folic acid supplementation:** “Treatment of anthracycline-resistant metastatic breast cancer with new antineoplastic agents remains a challenge. The 5-year survival for this disease is only 15%, and hormonal and chemotherapeutic options remain essentially palliative...The long time known 5-fluorouracil comes to the third place of the effective drugs. Continuous infusion or addition of folic acid increases the intracellular efficacy and results in 5-53% objective remissions.”<sup>13</sup>

Folic acid doubled survival rates for colon cancer patients: “In a prospective randomized multicentre trial 139 patients with metastatic colorectal carcinoma (70 men, 69 women; age 35-81 years) were given palliative treatment with fluorouracil (400 mg/m<sup>2</sup> daily for 5 days) alone or combined with folic acid (100 mg/m<sup>2</sup> before each dose of fluorouracil). Both groups were comparable in respect of age, sex, Karnofsky index and number of localisations of metastases. The criterion for starting the treatment was progression of the malignancy or clinical symptoms caused by the tumour. Resulting remission rates (fluorouracil monotherapy vs combination with folic acid) were: complete or partial remission, 9 vs 16%; arrest of tumour growth, 20 vs 60%; progression 71 vs 24%. Peripheral side effects, such as stomatitis and diarrhoea, were similarly frequent with the two treatment regimens and reasonably tolerable. Median survival time for the fluorouracil monotherapy was 7.24 months from onset of treatment, and 9.1 months from the time that any metastases were diagnosed. The combination treatment with folic acid achieved a significantly longer median survival time ( $P$  less than 0.0001), 14.98 months from treatment onset and 16.3 months from metastasis diagnosis. **The higher rate of response and the significantly prolonged survival time signify an improvement of the therapeutic profile of fluorouracil by addition of folic acid in the palliative therapy of colorectal carcinomas.**”<sup>14</sup>

## ANTIOXIDANTS:

**Vitamin E has been used to enhance radiation and chemotherapy treatments:** “This hypothesis was here tested in twelve patients with colorectal cancer (Dukes' C and D) who, prior to intervention with chemo- or radiotherapy, received a daily dose of 750 mg of vitamin E during a period of 2 weeks. RESULTS: Short-term supplementation with high doses of dietary vitamin E leads to increased CD4:CD8 ratios and to enhanced capacity by their T cells to produce the T helper 1 cytokines interleukin 2 and IFN-gamma. In 10 of 12 patients, an increase of 10% or more (average, 22%) in the number of T cells producing interleukin 2 was seen after 2 weeks of vitamin E supplementation, as compared with peripheral blood monocyte samples taken before treatment ( $P = 0.02$ ). Interestingly, there seemed to be a more pronounced stimulatory effect by vitamin E on naive (CD45RA(+)) T helper cells as compared with T cells with a memory/activated phenotype.

CONCLUSIONS: Dietary vitamin E may be used to improve the immune functions in patients with advanced cancer, as a supplement to more specific immune interventions.”<sup>15</sup>

“Selenium (Se) is an essential nutrient, and Se deficiency is associated with disease conditions and general impairment of the immune system. Supplementation of Se to humans already consuming the RDA may help to prevent certain cancers. A convincing argument can be made for augmenting the food supply with Se...”<sup>16</sup>

“Selenium is an essential trace element involved in several key metabolic activities via selenoproteins, enzymes that are essential to protect against oxidative damage and to regulate immune function. Selenium also may have other health benefits unrelated to its enzymatic functions. It may provide important health benefits to people whose oxidative stress loads are high, such as those with inflammatory or infectious diseases like rheumatoid arthritis or human immunodeficiency virus/acquired immunodeficiency syndrome, or who are at high risk for cancers, particularly prostate cancer. Some studies have generated compelling evidence that selenium is beneficial...”<sup>17</sup>

Regarding the use of the antioxidant red pigment Lycopene: “Quite surprising was the decrease in blood prostate-specific antigen, which was explained by the increase in apoptotic death of prostate cells, especially in carcinoma regions. Prostate cancer cell cultures (LNCaP) were also sensitive to lycopene in growth medium, which caused an increased apoptosis and arrested the cell cycle.”<sup>18</sup>

Regarding radiation and antioxidants: “It is very prudent to continue to support the well-established radiobiological concept that no radiation dose can be considered completely safe, and that all efforts must be made to reduce both the radiation dose and biological damage, no matter how small that damage might be, without sacrificing the benefits of radiation. Based on the results of many scientific experiments, **formulations containing multiple antioxidants for biological protection against radiation damage in humans can be developed, and this strategy together with the existing physical concept of radiation protection, should further reduce potential risks of low doses of ionizing radiation in humans.**”<sup>19</sup>

Vitamin E and breast cancer therapies: “Recent studies with alpha-TEA show it to be a potent inducer of apoptosis in a wide variety of epithelial cancer cell types, including breast, prostate, lung, colon, ovarian, cervical, and endometrial in cell culture, and to be effective in significantly reducing tumor burden and metastasis in a syngeneic mouse mammary tumor model, as well as xenografts of human breast cancer cells. **Studies also show that alpha-TEA, in combination with the cyclooxygenase-2 inhibitor celecoxib and the chemotherapeutic drug 9-nitro-camptothecin decreases breast cancer animal model tumor burden and inhibits metastasis significantly better than do single-agent treatments.**”<sup>20</sup>

**“A number of clinical studies have already demonstrated beneficial effects of antioxidants in ameliorating side effects of chemotherapy. More theoretical work on the chemistry of antioxidants and chemotherapy drugs suggests that antioxidants might improve therapeutic efficacy of antineoplastics by counteracting aldehydes that impede the passage of cells through the cell cycle.”**<sup>21</sup>

According to a report by the Agency for Healthcare Research and Quality (AHRQ): “Subgroup analysis did identify a statistically significant 9% reduction in all cause mortality and a borderline significant 13% reduction in all-cancer mortality associated with supplemental vitamin E in combination with other micro-nutrients.”<sup>22</sup>

A Tufts University review of antioxidants and human cancer stated: “...selenium and vitamin E reduced the risk of some forms of cancer, including prostate and colon cancer, and carotenoids have been shown to help reduce breast cancer risk. Cancer treatment by radiation and anticancer drugs reduces inherent antioxidants and induces oxidative stress, which increases with disease progression. **Vitamins E and C have been shown to ameliorate adverse side effects associated with free radical damage to normal cells in cancer therapy, such as mucositis and fibrosis, and to reduce the recurrence of breast cancer.**”<sup>23</sup>

**“Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity...** At present, there is no strategy to reduce the risk of recurrence of the primary tumors or of a second cancer among survivors. Patients unresponsive to standard or experimental therapies have little option except for poor quality of life for the remainder of life. Therefore, additional approaches should be developed to improve the efficacy of current management of cancer. In this review, the author proposes that an

active nutritional protocol that includes high doses of multiple dietary antioxidants and their derivatives (vitamin C, alpha-tocopheryl succinate, and natural beta-carotene), but not endogenously made antioxidants (glutathione- and antioxidant enzyme-elevating agents), when administered as an adjunct to radiation therapy, chemotherapy, or experimental therapy, may improve its efficacy by increasing tumor response and decreasing toxicity. This nutritional protocol can also be used when patients become unresponsive to standard therapy or experimental therapy to improve quality of life and possibly increase the survival time. The authors also propose that after completion of standard therapy and/or experimental therapy, a maintenance nutritional protocol that contains lower doses of antioxidants and their derivatives, together with modification in diet and lifestyle, may reduce the risk of recurrence of the original tumor and development of a second cancer among survivors. Experimental data and limited human studies suggest that use of these nutritional approaches may improve oncologic outcomes and decrease toxicity.<sup>24</sup>

**“Proanthocyanidin from grape seeds enhances anti-tumor effect of doxorubicin both in vitro and in vivo.”<sup>25</sup>**

In a recent study, the conclusion was that: **“Supplementation with high doses of alpha-tocopherol and beta-carotene during radiation therapy could reduce the severity of treatment adverse effects.”<sup>26</sup>**

CoEnzymeQ10 (CoQ10) enhanced the efficacy of tamoxifen: **“Administration of TAM along with CoQ10 restored the (antioxidant enzyme) activities to a significant level thereby preventing cancer cell proliferation.** This study highlights the increased antioxidant enzyme activities in relation to the susceptibility of cells to carcinogenic agents and the response of tumour cells to the chemotherapeutic agents.<sup>27</sup>

Selenium and Vitamin E enhanced the effects of cytostatic drugs: “Our observations regarding the role of antioxidant treatment suggest: 1) a benefic effect on DNA alkylant-induced lesions, expressed by a decrease in the level of 3H-Thymidine uptake in liver and, 2) an increase of the inhibitory activity of cytostatic on DNA replication biosynthesis in tumor cells, suggested by lower 3H-Thymidine incorporation in tumor cells. The most significant results were showed in both analyzed tissues, when the Orgasol 50 + Vitamin E administration begins at the same time with the tumor cell inoculation. **These findings clearly show the organic Se salts and Vitamin E constitute a valuable adjuvant in anticancer medication,** increasing the interest for the application of these antioxidants in cancer therapy and prevention.”<sup>28</sup>

**“Studies involving pentoxifylline plus vitamin E demonstrated regression in RIF. The combination was more effective than placebo and may be superior to monotherapy with either agent.”<sup>29</sup>**

“alpha-TS also enhances the growth-inhibitory effect of ionizing radiation, hyperthermia, some chemotherapeutic agents and biological response modifiers on tumor cells, while protecting normal cells against some of their adverse effects. Thus, **alpha-TS alone or in combination with dietary micronutrients can be useful as an adjunct to standard cancer therapy by increasing tumor response and possibly decreasing some of the toxicities to normal cells.**”<sup>30</sup>

In cancer patients a placebo-controlled, cross-over clinical trial using Lipid Replacement Therapy plus antioxidants demonstrated that the adverse effects of chemotherapy can be reduced in 57-70% of patients. **Dietary use of unoxidized membrane lipids plus antioxidants is recommended for patients undergoing cancer therapy to improve quality of life but should not be taken at the same time of day as the therapy.**<sup>31</sup>

#### REFERENCES:

1. Hardman WE. Omega-3 fatty acids to augment cancer therapy. J Nutr. 2002 Nov;132(11 Suppl):3508S-3512S. Review. PMID: 12421878
2. Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. Cancer. 1998 Jan 15;82(2):395-402. PMID: 9445198

3. Ross JA, Fearon KC. Eicosanoid-dependent cancer cachexia and wasting. *Curr Opin Clin Nutr Metab Care*. 2002 May;5(3):241-8. Review. PMID: 11953648
4. Hardman WE. (n-3) fatty acids and cancer therapy. *J Nutr*. 2004 Dec;134(12 Suppl):3427S-3430S. Review. PMID: 15570049
5. Chi TY, Chen GG, Lai PB. Eicosapentaenoic acid induces Fas-mediated apoptosis through a p53-dependent pathway in hepatoma cells. *Cancer J*. 2004 May-Jun;10(3):190-200. PMID: 15285929
6. Lai PB, Ross JA, Fearon KC, Anderson JD, Carter DC. Cell cycle arrest and induction of apoptosis in pancreatic cancer cells exposed to eicosapentaenoic acid in vitro. *Br J Cancer*. 1996 Nov;74(9):1375-83. PMID: 8912532
7. Rose DP, Connolly JM. Regulation of tumor angiogenesis by dietary fatty acids and eicosanoids. *Nutr Cancer*. 2000;37(2):119-27. Review. PMID: 11142082
8. Kenny FS, Pinder SE, Ellis IO, Gee JM, Nicholson RI, Bryce RP, Robertson JF. Gamma linolenic acid with tamoxifen as primary therapy in breast cancer. *Int J Cancer*. 2000 Mar 1;85(5):643-8. PMID: 10699943
9. Patrick Quillin, PhD, RD, CNS, Director of Nutrition, Cancer Treatment Centers of America. IAACN Symposium, Orlando, FL September 2005 "Endocrine Physiology of Healthy Glands & Hormones" - How Nutrients Affect the Endocrinology of Cancer (presentation)
10. Jatoi A, Daly BD, Kramer G, Mason JB. A cross-sectional study of vitamin intake in postoperative non-small cell lung cancer patients. *J Surg Oncol*. 1998 Aug;68(4):231-6. PMID: 9721708
11. Lamm DL, Riggs DR, Shriver JS, vanGilder PF, Rach JF, DeHaven JI. Megadose vitamins in bladder cancer: a double-blind clinical trial. *J Urol*. 1994 Jan;151(1):21-6. PMID: 8254816
12. Tallberg T, Uusitalo R, Sarna S, Seregard S, Werschnik C. Improvement of the recurrence-free interval using biological adjuvant therapy in uveal melanoma. *Anticancer Res*. 2000 May-Jun;20(3B):1969-75. PMID: 10928136
13. Kreienberg R. [Therapy of anthracycline-resistant metastatic breast carcinoma]. *Schweiz Rundsch Med Prax*. 1998 Apr 22;87(17):573-7. Review. German. PMID: 9623323
14. Loffler TM, Korsten FW, Reis HE, Planker M, Burghardt F, Aulbert E, Lindemann W, Schroder M, Hausamen TU, Strohmeier G. [Fluorouracil as monotherapy or combined with folinic acid in the treatment of metastasizing colorectal carcinoma]. *Dtsch Med Wochenschr*. 1992 Jun 26;117(26):1007-13. German. PMID: 1618109
15. Malmberg KJ, Lenkei R, Petersson M, Ohlum T, Ichihara F, Glimelius B, Frodin JE, Masucci G, Kiessling R. A short-term dietary supplementation of high doses of vitamin E increases T helper 1 cytokine production in patients with advanced colorectal cancer. *Clin Cancer Res*. 2002 Jun;8(6):1772-8. PMID: 12060616
16. Finley JW. United States Department of Agriculture, Agricultural Research Service, Grand Forks Human Nutrition Research Center. Selenium accumulation in plant foods. *Nutr Rev*. 2005 Jun;63(6 Pt 1):196-202. Review. PMID: 16028563
17. Ryan-Harshman M, Aldoori W. The relevance of selenium to immunity, cancer, and infectious/inflammatory diseases. *Can J Diet Pract Res*. 2005 Summer;66(2):98-102. Review. PMID: 15975198
18. Stacewicz-Sapuntzakis M, Bowen PE. Role of lycopene and tomato products in prostate health. *Biochim Biophys Acta*. 2005 May 30;1740(2):202-5. Epub 2005 Mar 13. Review. PMID: 15949687
19. Prasad KN. Rationale for using multiple antioxidants in protecting humans against low doses of ionizing radiation. *Br J Radiol*. 2005 Jun;78(930):485-92. Review. PMID: 15900053
20. Kline K, Yu W, Sanders BG. Vitamin E and breast cancer. *J Nutr*. 2004 Dec;134(12 Suppl):3458S-3462S. Review. PMID: 15570054
21. Block KI. Antioxidants and cancer therapy: furthering the debate. *Integr Cancer Ther*. 2004 Dec;3(4):342-8. Review. PMID: 15523105
22. Shekelle P, Hardy ML, Coulter I, Udani J, Spar M, Oda K, Jungvig LK, Tu W, Suttorp MJ, Valentine D, Ramirez L, Shanman R, Newberry SJ. Effect of the supplemental use of antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cancer. *Evid Rep Technol Assess (Summ)*. 2003 Oct;(75):1-3. Review. PMID: 15523748
23. Borek C. Dietary antioxidants and human cancer. *Integr Cancer Ther*. 2004 Dec;3(4):333-41. Review. PMID: 15523104
24. Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. *Integr Cancer Ther*. 2004 Dec;3(4):310-22. Review. PMID: 15523102
25. Zhang XY, Bai DC, Wu YJ, Li WG, Liu NF. Proanthocyanidin from grape seeds enhances anti-tumor effect of doxorubicin both in vitro and in vivo. *Pharmazie*. 2005 Jul;60(7):533-8. PMID: 16076082
26. Bairati I, Meyer F, Gelinat M, Fortin A, Nabid A, Brochet F, Mercier JP, Tetu B, Harel F, Abdous B, Vigneault E, Vass S, Del Vecchio P, Roy J. Randomized trial of antioxidant vitamins to prevent acute

- adverse effects of radiation therapy in head and neck cancer patients. *J Clin Oncol*. 2005 Aug 0;23(24):5805-13. Epub 2005 Jul 18. PMID: 16027437
27. Perumal SS, Shanthy P, Sachdanandam P. Combined efficacy of tamoxifen and coenzyme Q10 on the status of lipid peroxidation and antioxidants in DMBA induced breast cancer. *Mol Cell Biochem*. 2005 May;273(1-2):151-60. PMID: 16013450
  28. Mihalache D, Preoteasa V, Barca V. Effects of combined selenium and vitamin E administration on DNA in Walker tumor bearing Wistar rat exposed to cytostatic acute treatment. *Roum Arch Microbiol Immunol*. 2003 Jul-Dec;62(3-4):239-50. PMID: 16008147
  29. Chiao TB, Lee AJ. Role of pentoxifylline and vitamin E in attenuation of radiation-induced fibrosis. *Ann Pharmacother*. 2005 Mar;39(3):516-22. Epub 2005 Feb 8. Review. PMID: 15701781
  30. Prasad KN, Kumar B, Yan XD, Hanson AJ, Cole WC. Alpha-tocopheryl succinate, the most effective form of vitamin E for adjuvant cancer treatment: a review. *J Am Coll Nutr*. 2003 Apr;22(2):108-17. Review. PMID: 12672706
  31. Nicolson GL. Lipid replacement/antioxidant therapy as an adjunct supplement to reduce the adverse effects of cancer therapy and restore mitochondrial function. *Pathol Oncol Res*. 2005;11(3):139-44. Epub 2005 Sep 29. PMID: 16195767