ANTIOXIDANTS AND OTHER NUTRIENTS DO NOT INTERFERE WITH CHEMOTHERAPY OR RADIATION THERAPY AND CAN INCREASE KILL AND INCREASE SURVIVAL, PART 2

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Purpose • Some in the oncology community contend that patients undergoing chemotherapy and/or radiation therapy should not use food supplement antioxidants and other nutrients. Oncologists at an influential oncology institution contended that antioxidants interfere with radiation and some chemotherapies because those modalities kill by generating free radicals that are neutralized by antioxidants, and that folic acid interferes with methotrexate. This is despite the common use of amifostine and dexrazoxane, 2 prescription antioxidants, during chemotherapy and/or radiation therapy.
Design • To assess all evidence concerning antioxidant and other nutrients used concomitantly with chemotherapy and/or radiation therapy. The MEDLINE® and CANCERLIT® databases were searched from 1965 to November 2003 using the words *vitamins, antioxidants, chemotherapy,* and *radiation therapy*. Bibliographies of articles were searched. All studies reporting concomitant nutrient use with chemotherapy and/or radiation therapy (280 peer-reviewed articles including 62 in vitro and 218 in vivo) were indiscriminately included.
Results • Fifty human clinical randomized or observational trials have been conducted, involving 8,521 patients using beta-carotene; vitamins A, C, and E; selenium; cysteine; B vitamins; vitamin D_3; vitamin K_3; and glutathione as single agents or in combination.
Conclusions • Since the 1970s, 280 peer-reviewed in vitro and in vivo studies, including 50 human studies involving 8,521 patients, 5,081 of whom were given nutrients, have consistently shown that do not interfere with therapeutic modalities for cancer. Furthermore, non-prescription antioxidants and other nutrients enhance the killing of therapeutic modalities for cancer, decrease their side effects, and protect normal tissue. In 15 human studies, 3,738 patients who took non-prescription antioxidants and other nutrients actually had increased survival.
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Two of every 5 Americans will develop cancer, and the incidence of most cancers has increased annually since 1930.[1-5] In addition, since 1930, despite the use of radiation therapy, chemotherapy, immunotherapy, and improved surgical and diagnostic techniques, there has been limited progress in cancer survival for most adult cancers.[1-5] Chemotherapy and radiation therapy, however, continue to have a large role in cancer treatment but produce great morbidity. Two prescription medicines, amifostine and dexrazoxane, both antioxidants, reduce cancer therapy side effects without interfering with antitumor killing.

A single, front-page interview in *The New York Times* in 1997, which was not based on published scientific work,[6] and a single research paper involving mice, along with a press release by its author in 1999,[7] led to the erroneous notion that vitamin C interferes with chemotherapy and radiation in humans. This notion soon applied to all antioxidants as physicians, patients, the media, the American Cancer Society,[8,9] and scores of websites took the same position without reviewing the scientific evidence. Methods have been presented in Part 1. Part 2 reviews data about antioxidant combinations, B vitamins, vitamins D_3 and K_3, and the glutathione-selenium complex. A summary and discussion are presented.

REVIEW OF STUDIES

Antioxidant Combinations

In an observational study, 58 children with various cancers were treated with chemotherapy appropriate for their site and total parenteral nutrition (TPN) that contained antioxidants, nutrients, fats, protein, glucose, and electrolytes. A 36% response rate was obtained for these patients, who otherwise would have been denied adequate chemotherapy because of fear of complications from malnutrition. Compared to historical controls, patients in this study had few side effects and a higher response rate.[10]

In an observational study, 41 children with various cancers (Wilm's tumor, hepatic cancer, leukemia, lymphoma, primary bone cancer, and others) were treated with chemotherapy and radiation therapy appropriate for their site and TPN that contained antioxidants, nutrients, protein, fats, glucose, and electrolytes. Twenty-one children were able to continue their chemotherapy treatment at full dose without interruption while being administered TPN. Compared to historical controls, patients in this study had few side effects and a higher response rate.[11]

In another observational study, 18 patients with small cell lung cancer were treated with cyclophosphamide, doxorubicin HCL (adriamycin), vincristine chemotherapy, and/or irradiation at regular intervals. Their serum was analyzed for nutrient levels. In doses based on the serum analysis, all patients were given the following daily supplements of vitamins and minerals: 15,000-40,000 IU vitamin A; 10,000-20,000 IU beta-carotene; 300-800 IU vitamin E; 150-750 mg thiamin; 15-50 mg riboflavin; 200-1,140 mg pyridoxide; 0.03-1.60 mg vitamin B_{12}; 150-400 mg nicotinamide; 400-1,000 IU vitamin D; 2,000-5,000 mg vitamin C; 50-300 mg calcium; 0.3-10 mg biotin. The administration of these vitamins and minerals during chemotherapy and/or irradiation prolonged survival, decreased side effects, and increased response rates when compared to historical controls in the literature of patients who received only chemotherapy and radiation without vitamins and minerals. In this study, patients who had increased survivals started antioxidants before treatment began.[12]

In an observational study of 32 patients with breast cancer that spread to axillary lymph nodes, patients were given conventional surgical and therapeutic treatments, as well as daily supplements of vitamin C (2,850 mg), vitamin E (2,500 IU), beta-carotene (32.5 IU), selenium (387 µg), essential fatty acids (1.2 g gamma linolenic acid and 3.5 g omega-3 fatty acids), and coenzyme Q10 (90 mg). Compared to patients who received conventional treatment only, this group had decreased rates of recurrence and increased quality of life, survival rates, and partial remission rates.[13]

In an observational study of 63 patients with oral squamous cell carcinoma, participants received inductive concomitant chemoradiotherapy with cobalt 60 (30Gy), peplomycin (38 mg), and 5-fluorouracil (3,500 mg), as well as daily doses of vitamin C (500 mg), vitamin E (200 IU), and glutathione (200 mg). Patients were also given azelastine, an antihistamine (2 mg/day). Patients experienced an increased response rate and a greater reduction in the severity of side effects from the chemoradiotherapy.[14]

In another study, 41 patients with unresectable or metastatic gastric cancer were randomized to receive supportive care or 5-fluorouracil (1,500 mg/m^2) and methotrexate (1,500 mg/m^2) on day 1, leukovorin rescue (30 mg every 6 hours for 48 hours) and epirubicin (60 mg/m^2) on day 15. All patients received vitamins A (9,000 IU) and E (210 mg) daily. Compared to historical controls treated with the same chemotherapy regimen, the administration of vitamins A and E increased patient survival slightly.[15]

In an observational study of 17 patients with squamous cell carcinoma of the upper aerodigestive tract, patients were treated with radiotherapy, antioxidants, and beta-alanine, an amino acid. They were followed for 63 months and found to have decreased side effects from radiotherapy, improved physical comfort, and increased survival compared to a reference population of patients with squamous cell carcinoma of the upper aerodigestive tract.[16]

In an observational study of 20 patients with various metastatic cancers (lymphoma, leukemia, Hodgkin's, multiple myeloma, sarcoma, lung, pancreatic, kidney, colon, melanoma, and breast), patients were treated with chemotherapy appropriate for their site. During and after chemotherapy, they were given 4 doses a day each of vitamin A (100,000 IU), vitamin E (800 IU), and vitamin C (2 g). The complete and partial response rate (greater than 50% reduction in mass) was 75%—significantly higher than the expected 40%. Side effects were also decreased with this vitamin regimen.[17]

In an observational study of 10 patients with various cancers (lymphoma, breast, lung, esophageal, head and neck, colon, and choriocarcinoma), participants were treated with chemotherapy appropriate for their site. After the chemotherapy produced profound side effects (eg, nausea; vomiting; depression of neutrophils, platelets, red cells), nutrients, including selenium and vitamins A, C, and E, were added to the treatment program. Absolute neutrophil and platelet counts were significantly higher when the nutrients were added, allowing for decreased side effects.[18]

In a randomized study of 24 patients with various cancers who received either chemotherapy (14 patients) or radiation therapy (10 patients), participants were randomized to receive placebo or antioxidants (N-acetylcysteine and vitamins E and C). As determined by ejection fraction, antioxidants protected the heart from the damage of chemotherapy and radiation therapy. The left ventricular ejection fraction dropped significantly in patients receiving placebo (radiation therapy: 67% down to 56%; chemotherapy: 67% down to 60%), whereas patients receiving antioxidants showed limited decreases in the ejection fraction (radiation therapy: 63% down to 61%; chemotherapy: 67% down to 64%).[19]

B Vitamins

In a randomized study of 25 patients with locally advanced breast cancer, head and neck cancers, or melanoma, patients were treated with radiation and hyperthermia. They were randomized to receive nicotinamide (up to 9 g) by mouth 1 hour before treatments in an attempt to increase blood flow around the tumor. Nicotinamide decreased side effects and produced a complete response in 72% and an overall response rate of 88% (complete and partial responses). Those who achieved a complete response (72%) did not have a recurrence at the treatment site for as long as the patients were followed (time not defined by study authors).[20]

In a randomized study of 6,300 patients with gynecological and breast cancers treated from 1960 to 1988 with chemotherapy appropriate for their site, patients were randomized to receive pyridoxine (300 mg per day) during radiation, as the author had documented that radiation decreased serum nutrient levels of pyridoxine and other nutrients. Those who received pyridoxine had a 15% higher 5-year survival, fewer side effects, and a higher response rate.[21]

In another study, 248 patients with stage III or stage IV ovarian epithelial cancer were randomized to receive cisplatin (37.5 mg/m^2 or 75 mg/m^2 intravenously on day 1) and hexamethylmelamine (200 mg/m^2 orally on days 8-21) with or without oral pyridoxine (300 mg/m^2) administration on days 1-21. Pyridoxine administration significantly reduced neurotoxicity.[22]

Vitamin D_3

In an observational study, 44 patients with high-risk primary myelodysplastic syndromes and an excess of marrow blasts were treated with a combination of low-dose cytosine arabinoside (Ara-C; 10 mg/m^2), retinoic acid (20 mg/m^2/d), and vitamin D_3 (0.75 mg/d) until relapse or death. A matched control group of 44 additional patients was given supportive therapy only. The intervention group had a higher overall response rate (50% compared to 20%) and a significantly better survival rate than the control group and treated historical controls from other series (40% compared to 10%, $P<.0001$).[23]

Vitamin K_3

In an observational study, 51 patients with various refractory solid tumors were treated with a 48-hour continuous intravenous infusion of vitamin K_3 (menadione; 1.0 to 3 g/m^2), followed by a bolus of mitomycin C (5-20 mg/m^2). In this study, menadione decreased side effects and increased the response rate.[24]

In another observational study, 14 patients with various advanced cancers (7 patients with chronic lymphocytic leukemia, and 1 patient each with lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, multiple myeloma, breast, ovary, and small cell lung cancer) were treated with 18 courses of vitamin K_3 (40-3,200 mg/m^2 per course administered over 1 to 4 days) and various combinations of cytotoxic drugs appropriate for their site. The cytotoxic agents included carmustine, cyclophosphamide, dexamethasone, doxorubicin, melphalan, nitrogen mustard, platinum, vinblastine, and vincristine. Menadione increased the response rate and decreased the side effects of chemotherapy, possibly by altering drug-resistance profiles.[25]

Glutathione

In an observational study of 50 consecutive patients with untreated stage III or stage IV ovarian cancer, patients were treated with 2 cycles of cisplatin (40 mg/m^2), carboplatin (60 mg/m^2), and glutathione (2,500 mg before chemotherapy), followed by debulking surgery where possible and 3 more cycles of chemotherapy and glutathione. Fifty-four percent of patients had a complete response, there were fewer side effects, and survival was better than expected (median survival >48 months).[26]

In another observational study, 12 patients with stage III ovarian cancer and 23 patients with localized disease at high risk for recurrence were treated for 3 weeks with cisplatin (90 mg/m^2 intravenously over 30 minutes) and cyclophosphamide (600 mg/m^2 intravenously). Glutathione (5 g in 200 mL of normal saline) was administered 15 minutes before cisplatin treatments by short-term fusion. In addition to decreasing cisplatin-associated toxicity, glutathione optimized efficacy of cisplatin treatment. At the conclusion of the treatments, all but 2 of the stage III patients had complete pathological responses, and all of the high-risk patients remained disease-free. There was no renal impairment or neurotoxicity.[27]

In a randomized study, 50 patients with advanced gastric cancer were treated with a weekly cisplatin-based regimen. Patients in the intervention group received 1.5 g/m^2 of glutathione in 100 mL of normal saline 15 minutes before cisplatin treatment and 600 mg of glutathione by intramuscular injection on days 2 and 5. After 15 weeks of treatment, only 4 of the 24 patients randomized to receive glutathione suffered from neurotoxicity, as compared to 16 of 18 patients in the placebo (normal saline) group. Glutathione also reduced hemotransfusion requirements (62% in the intervention group vs 32% in the control group). Although glutathione reduced treatment toxicity, it did not reduce the clinical activity of the cisplatin-based chemotherapy. In fact, patients receiving glutathione had a higher response rate (76%) than patients in the placebo group (52%).[28]

In an observational study, 11 previously untreated patients with metastatic colorectal cancer were given 5-fluorouracil (750 mg/m^2 on days 1-5) and cisplatin (40 mg/m^2 on days 6-8) every 4 weeks. Glutathione (2.5 g) was administered intravenously before each cisplatin infusion. Side effects from treatment were reduced without altering the response rate.[29]

In another observational study, 79 patients with advanced stage III or stage IV ovarian cancer were treated with high-dose cisplatin (40 mg/m^2), glutathione (2,500 mg as a short-term infusion prior to cisplatin), and cyclophosphamide (600 mg/m^2). After a total of 345 courses, 57% of patients achieved complete clinical responses, and 25% had partial remissions (an 82% overall response rate). Toxicity of the regimen was moderate, and the severity of peripheral neurotoxicity and ototoxicity was less than has been reported with similar high-dose cisplatin regimens without glutathione administration.[30]

Forty patients with stage III or stage IV ovarian carcinoma in an observational study were treated with glutathione (1,500 mg/m^2) over 15 minutes before cisplatin (40 mg/m^2 days 1-4) and cyclophosphamide (600 mg/m^2 on day 4) treatments. Treatment was repeated every 3 to 4 weeks. After 5 courses of treatment, 62% of patients achieved complete clinical remission, and the overall response rate was 86%. Glutathione prevented renal impairment, allowed for an improved toleration to the high-dose cisplatin treatment, and increased the response rate of the treatment.[31]

In another observational study, 27 patients with bulky, operable cervical cancer (stage IB/II) were given 1 course of cisplatin (40 mg/m^2 for 5 consecutive days) with glutathione protection and bleomycin (15 mg on days 2, 8, and 9). One month later, 21 patients had objective responses that made surgery easier. There were also fewer side effects from treatment.[32]

In another observational study, 12 patients with either non-small cell lung cancer or pleural mesothelioma were given 2 courses of cisplatin (80 mg/m^2) by infusion every 3 to 4 weeks. Six of these patients were pretreated with glutathione (2.5 g intravenously) 15 minutes before cisplatin treatment. These patients had higher response rates and fewer side effects than patients who were not given glutathione protection.[33]

Twenty patients with advanced ovarian carcinoma were treated every 21 to 28 days with cisplatin (45 mg/m^2 intravenously on days 1 and 2), cyclophosphamide (900 mg/m^2 intravenously on day 2), and glutathione (2,500 mg intravenously over 15 minutes, before cisplatin treatment) in an observational study. Compared to patients with similar conditions who received similar treatments without glutathione, patients in this study had decreased nephrotoxicity and neurotoxicity. Furthermore, glutathione improved the efficacy of treatment in these patients, producing a pathological complete response rate of 55% and a median survival of 26.5 months. Five patients were still alive and disease-free at 35 months.[34]

Thirteen patients with various cancers (sarcomas, breast, renal, histiocytoma, and Schwannoma) underwent treatment every 4 weeks with cyclophosphamide (1 hour infusion in escalating doses from 1.2 to 1.6 g/m^2) and glutathione (administered intravenously in 2 divided doses of 2.5 g in 100 mL normal saline 15 minutes before and 30 minutes after cyclophosphamide treatment) in this observational study. Glutathione protected against cyclophosphamide-induced urotoxicity and bladder damage without interfering with the efficacy of the cyclophosphamide.[35]

In another observational study, 15 patients with ovarian cancer and 1 with unknown adenocarcinoma were treated for a maximum of 5 consecutive courses with cisplatin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) with or without glutathione (1,500 mg/m^2) before each cisplatin treatment. Glutathione reduced the severity of myelosuppression and nephrotoxicity without interfering with the efficacy of treatment.[36]

In a randomized study, 36 patients with advanced ovarian cancer were treated every 4 weeks with cisplatin (40 mg/m^2). Patients who were randomized to receive glutathione (1.5 g/m^2 given by infusion over 15 minutes before cisplatin treatment) experienced less ototoxicity and other side effects. There were no differences in response rates between the groups.[37]

In an observational study by Plaxe et al, 16 patients with various advanced cancers in a phase I trial were given escalating doses of cisplatin (up to 125 mg/m^2) and glutathione (3 g/m^2 fixed dose) every 21 days. Evaluation after 44 cycles of treatment indicated that glutathione reduced nephrotoxicity, ototoxicity, and other side effects of cisplatin. Glutathione also allowed an increase to 175% of cisplatin dose intensity.[38]

In a large observational study by Smyth et al, 151 patients with ovarian cancer were divided into 2 groups. The intervention group was given cisplatin (100 mg/m^2) and glutathione (2.5 g before cisplatin), and the control group received only cisplatin at the same dose. Patients given glutathione had less toxicity from cisplatin and were better able to tolerate 6 cycles of treatment (58% compared to 39% of patients in the control group). Patients who received glutathione also had significant improvements in depression, emesis, peripheral neurotoxicity, hair loss, shortness of breath, and difficulty concentrating. Furthermore, patients in the glutathione group had better responses to treatment and improved quality of life.[39]

DISCUSSION

For patients undergoing chemotherapy and/or radiation therapy, physicians are comfortable with and commonly use 2 prescription antioxidants, amifostine and dexrazoxane, for their proven benefits of reducing side effects and increasing response rates without interfering with the antitumor killing of the therapy. However, physicians often tell patients not to take food supplement antioxidants and nutrients because 2 individuals from a trusted institution stated that nonprescription nutrients interfere with cancer therapies. Also, the authors of a recent randomized study concluded that "supplementation with antioxidants reduced the severity of treatment side effects but might compromise radiation therapy efficacy."[40] Of the 540 head and neck cancer patients treated with radiation, 273 were given 400 IU dl-alpha-tocopherol during radiation and for 3 years after, and 77 patients of these 273 were given 30 mg beta-carotene during radiation and thereafter ranging from a total of 21 days to 609 days. There were no data presented to support the issue of local recurrence that occurred in 103 patients, half of whom recurred during the first year. We don't know if the local recurrence was in the field of radiation, within 2 cm of the field, or outside the field altogether but in the vicinity. However, we do know there was no difference in survival as per their Kaplan-Meier curves. This paper, without objective supporting data, added to the controversy that antioxidants might compromise radiation efficacy.

Many of the food supplement nutrients used in the above studies are antioxidants, molecules that neutralize free radicals. Most cancer modalities exert their cancer killing effects by generating free radicals. Therefore, it would seem inconsistent that antioxidants could help cancer patients. However, since the 1970s, 280 peer-reviewed studies (62 in vitro and 218 in vivo) have been published (Figure), including 50 human clinical studies that used non-prescription antioxidants and other nutrients (8,521 patients, 5,081 of whom were given nutrients) and 50 studies on prescription antioxidants. These studies have consistently

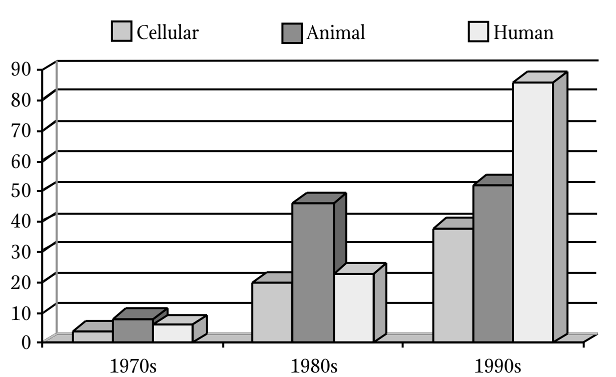

FIGURE Studies on Nutrients in Cellular, Animal, and Human Cancer Published in Three Decades

TABLE The Effects of Nutrients on Patients Receiving Systemic Treatment and/or Radiation Treatment

Author (reference)	Type of Study	Number of Patients, Cancer Type	Nutrient	Systemic Treatment	Local Treatment	Higher Response Rate	Decreased Side Effects	Increased Survival
Israel (41)	Randomized	100, breast	A	Chemotherapy, 5-fluorouracil, bleomycin, doxorubicin HCL, Mitomycin	None	Yes	Yes	Yes
Komiyama (42)	Observational	275, head/neck	A	5-fluorouracil	Radiation therapy	Yes	Yes	Not addressed
Meyskens (43)	Randomized	153, CML	A	Busulfan	None	Yes	Yes	Yes
Recchia, De Filippis (44)	Observational	40, lung	A	Cisplatin, vindesine, 5-fluorouracil, interferon	None	Yes	Yes	Yes
Recchia, Lelli (45)	Observational	23, oral	A	5- fluorouracil, cisplatin	None	Yes	Yes	Yes
Recchi, Rea (46)	Observational	36, breast	A	Chemotherapy, 5-fluorouracil, VCR, doxorubicin prednisone, interferon, tamoxifen	None	Yes	Yes	Yes
Recchia, Serafin (47)	Observational	22, pancreas	A	5-fluorouracil, epirubicin, mitomycin C, interferon Tamoxifen, interferon	None	No difference	No difference	No difference
Recchia, Sica (48)	Observational	49, breast	A	Vincristine, methotrexate, bleomycin	None	Yes	Yes	Yes
Mills (49)	Randomized	20, mouth	Carotene	Chemo (site appropriate)	Radiation therapy	No difference	Yes	No difference
Santamaria (50)	Observational	15, various	Carotene	13-cis-retinoic acid	Radiation therapy	Yes	Yes	Yes
Besa (51)	Observational	66, myelodysplasia	E	13-cis-retinoic acid	None	Yes	Yes	Yes
Dimery (52)	Observational	39, head/neck, skin, lung	E	All-trans- retinoic acid, erythropoietin	None	Not addressed	Yes	Not addressed
Ganser (53)	Observational	17, myelodysplasia	E	None	None	Yes	Yes	Not addressed
Gottlober (54)	Observational	1, benign	E	None	Radiation therapy	Yes	Yes	Not applicable
Legha (55)	Observational	21, breast metastasis	E	Cyclophosphamide, doxorubicin, HCL, fluorouracil	None	No difference	No difference	Not addressed
Lenzhofer (56)	Randomized	12, breast metastasis	E Nifedipine	Doxorubicin HCL	None	Yes	Yes	Not addressed
Lopez (57)	Randomized	20, leukemia	E	Chemotherapy for acute myelogenous, leukemia, transplant	None	Yes	Yes	Not addressed
Wadleigh (58)	Randomized	18, various	E	Chemotherapy (site appropriate)	None	Not addressed	Yes	Not addressed
Weitzman (59)	Randomized	16, various	E	Doxorubicin HCL regimen	None	No difference	No difference	Not addressed
Wood (60)	Observational	16, various	E	Doxorubicin HCL	None	Not addressed	Yes	Not addressed
Copeland (10)	Observational	58, various	Antioxidant Nutrients	Chemotherapy (site appropriate)	None	Yes	Yes	Not addressed

TABLE The Effects of Nutrients on Patients Receiving Systemic Treatment and/or Radiation Treatment (continued)

Author (reference)	Type of Study	Number of Patients, Cancer Type	Nutrient	Systemic Treatment	Local Treatment	Higher Response Rate	Decreased Side Effects	Increased Survival
Jaakkola (12)	Observational	18, small cell lung	Antioxidants Nutrients	Cyclophosphamide, doxorubicin HCL, vincristine	Radiation therapy	Yes	Yes	Yes
Lockwood (13)	Observational	32, breast	C, E, carotene, selenium	Chemotherapy	Radiation therapy	Yes	Yes	Yes
Osaki (14)	Observational	63, oral	C, E, glutathione	5-fluorouracil, peplomycin	Radiation therapy	Yes	Yes	Not addressed
Pyrhonen (15)	Randomized	41, gastric	A, E	Fluorouracil, epidoxorubicin, methotrexate	None	Not addressed	Yes	Yes
Rougereau (16)	Observational	17, oral, esophageal	Antioxidants	None	Radiation therapy	Yes	Yes	Yes
Sakamoto (17)	Observational	20, various	A, C, E	Chemotherapy (site appropriate)	None	Yes	Yes	Not addressed
Thiruvengadam (18)	Observational	10, various	A, E, C, Selenium	Chemotherapy (site appropriate)	None	Not addressed	Yes	Not addressed
Wagdi (19)	Randomized	24, various	Acetyl cysteine, E,C	Chemotherapy (site appropriate)	Radiation therapy	Not addressed	Yes	Not addressed
Kim (20)	Randomized	25, head/neck, melanoma	Nicotinamide	None	Radiation therapy, hyperthermia	Yes	Yes	Not addressed
Ladner (21)	Randomized	6,300,gyneco-logic, breast	High dose Pyridoxine	Chemotherapy (site appropriate)	Radiation therapy	Yes	Yes	Yes
Wiernik (22)	Randomized	248, ovarian	High dose Pyridoxine	Cisplatin, hexamethylamine	None	Not addressed	Yes	Not addressed
DeRosa (23)	Observational	44, myelodysplasia	Retinoic acid, D_3	Cytosine arabinoside	None	Yes	Yes	Yes
Margolin (24)	Observational	51, various	K_3	Mitomycin C	None	Yes	Yes	Not addressed
Nagoumey (25)	Observational	14, various	K_3	Chemotherapy (site appropriate)	None	Yes	Yes	Not addressed
Bohm, Oriana (26)	Observational	50, ovarian	Glutathione	Cisplatin, carboplatin	Surgery debulk	Yes	Yes	Yes
Bohm, Battista Spatti (27)	Observational	35, ovarian	Glutathione	Cisplatin, cyclophosphamide	None	Yes	Yes	Not addressed
Cascinu (28)	Randomized	50, gastric	Glutathione	Cisplatin	None	Yes	Yes	Not addressed
Cozzaglio (29)	Observational	11, colon	Glutathione	5-fluorouracil, cisplatin	None	Not addressed	Yes	Not addressed
Di Re (30)	Observational	79, ovarian	Glutathione	Cisplatin, cyclophosphamide	None	Yes	Yes	Not addressed
Di Re (31)	Observational	40, ovarian	Glutathione	Cisplatin, cyclophosphamide	None	Yes	Yes	Not addressed
Fontanelli (32)	Observational	27, cervical	Glutathione	Cisplatin, bleomycin	Surgery	Yes	Yes	Not addressed
Leone (33)	Observational	12, lung	Glutathione	Cisplatin	None	Yes	Yes	Not addressed

TABLE The Effects of Nutrients on Patients Receiving Systemic Treatment and/or Radiation Treatment (continued)								
Author (reference)	Type of Study	Number of Patients, Cancer Type	Nutrient	Systemic Treatment	Local Treatment	Higher Response Rate	Decreased Side Effects	Increased Survival
Locatelli (34)	Observational	20, ovarian	Glutathione	Cisplatin	None	Yes	Yes	Not addressed
Nobile (35)	Observational	13, various	Glutathione	Cyclophosphamide	None	Not addressed	Yes	Not addressed
Oriana (36)	Observational	16, ovarian, adenocarcinoma	Glutathione	Cisplatin, cyclophosphamide	None	Not addressed	Yes	Not addressed
Parnis (37)	Randomized	36, ovarian	Glutathione	Cisplatin	None	Not addressed	Yes	Not addressed
Plaxe (38)	Observational	16, various	Glutathione	Cisplatin	None	Not	Yes	Not
Plaxe (38)	Observational	16, various	Glutathione	Cisplatin	None	Not addressed	Yes	Not addressed
Smyth (39)	Observational	151, ovarian	Glutathione	Cisplatin	None	Yes	Yes	Not

shown that non-prescription antioxidants and other nutrients do not interfere with cancer therapeutic modalities. In addition, non-prescription antioxidants and other nutrients enhance the killing of cancer therapeutic modalities, decrease their side effects, and protect normal tissues, and in 15 human studies, 3,738 patients actually had prolonged survival.

Cancer cells accumulate excessive amounts of antioxidants due to a loss of the homeostasis control mechanism for the uptake of these nutrients.[61] Normal cells do not have this membrane defect and do not accumulate large amounts of antioxidants. Accumulation of excessive antioxidants and nutrients in cancer cells can shut down the oxidative reactions necessary for generating energy. In addition, dietary antioxidants also produce biological effects on cancer cells that are not related to antioxidant action, as outlined here.

1. Antioxidants increase cancer cell differentiation and/or apoptosis, and growth inhibition.[62,63]
   a. Antioxidants inhibit gene expression and/or activity of p53 mutant, c-myc, H-ras, Bcl_2, c-neu, c-erbB_2, vascular endothelial growth factor (VEGF), phosphotyrosine kinase, and protein kinase C.
   b. Antioxidants enhance gene expression and/or activity of p53 wild-type, p21, c-fos, c-jun, HSP70, HSP90, connexin, transforming growth factor beta (TGFb), mitogen-activated protein (MAP) kinase, caspase, and cyclin A and D and their kinases.
2. Antioxidants selectively inhibit repair of radiation damage of cancer cells but protect normal cells when antioxidants are used before, during, and after radiation—there are no published studies that show antioxidants protect cancer cells against radiation.[64]
3. Vitamin E reduces the expression of VEGF and thus acts as an anti-angiogenic factor.

With higher levels of intracellular accumulation of nutrients by cancer cells, more of these cellular alterations occur. These changes can lead to higher rates of cancer cell death and reduced rates of cell proliferation and induction of differentiation. These acquired changes of cancer cells that result from high doses of nutrients apparently override any protective action that antioxidants have against free radical damage on cancer cells and account for what is demonstrated in the international literature about this subject. Non-prescription antioxidants and other nutrients do not interfere with cancer therapeutic modalities, enhance their killing capabilities, decrease their side effects, or protect normal tissues, and in 15 human studies, 3,738 patients actually had prolonged survival. Antioxidant and other nutrient food supplements are safe and can help to enhance cancer patient care.

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