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REVIEW ARTICLE

Antioxidants and Cancer Therapy: A Systematic Review

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ABSTRACT

Purpose
Many patients with cancer take antioxidant nutritional supplements during cancer treatment to alleviate treatment toxicities and to improve long-term outcomes, but little is known about the efficacy and safety of antioxidant use during cancer treatment. We reviewed English-language manuscripts published in the biomedical literature, reporting the results of observational studies of antioxidant status and cancer outcomes and of intervention trials of antioxidants among patients receiving chemotherapy with or without radiation for various malignancies.

Methods
We searched the Medline database and the bibliographies of the retrieved manuscripts, reviews, and books on antioxidants and cancer. The retrieved studies are grouped by study design, malignancy, and end points.

Results
More than 100 citations were retrieved; 52 met our criteria, 31 were observational studies, and 21 were intervention trials. The studies varied in study design, timing of observation/intervention, intervention protocol, malignancy, and anticancer regimen.

Conclusion
These inconsistencies preclude a definitive conclusion as to the effect of chemotherapy on antioxidant status in patients undergoing anticancer therapy. However, our review suggests that total antioxidant status (measured by total radical antioxidant parameter) declines during cancer treatment. Adequately powered trials or observational studies among patients with a specific cancer diagnosis receiving a specific treatment regimen are needed to address patients' and physicians' concerns regarding these associations.

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INTRODUCTION

Recent surveys of patients with cancer have demonstrated that many (25% to 84%) use nutritional supplements containing antioxidants, often at doses higher than the recommended dietary allowances [1-3]. Patients with cancer take antioxidant supplements during or after conventional cancer treatment to enhance the benefits of treatment, to alleviate side effects, and/or to maintain or improve general health and well-being. However, the evidence that any antioxidant supplement has efficacy for any of those purposes is sparse and largely indirect.

In vitro and in vivo data suggest that certain antioxidants selectively inhibit the growth of tumor cells, may induce cellular differentiation, and may alter the intracellular redox state, thereby enhancing the effects of cytotoxic therapy [4-8]. Some investigators have argued that average concentrations of antioxidants may not be sufficient to counter the higher production of reactive oxygen metabolites, and may therefore promote cell proliferation and malignant progression [9]. Moreover, the suggestion of an association between beta carotene intake and increased risk of lung cancer in two lung cancer chemoprevention trials has generated concern about the cancer promoting effects of antioxidants [10,11]. Antioxidants may also reduce certain types of toxicity associated with chemotherapy, but it is feared

that they may do so by interfering with the efficacy of conventional therapy [12,13].

A rationale for antioxidant supplementation during chemotherapy is to compensate for treatment- or cancer-induced antioxidant depletion. The evidence for such depletion is limited. Some studies have explored the effect of conventional therapy on antioxidant status (as measured by serum micronutrients and/or total antioxidant capacity) in patients with cancer diagnoses. Others have explored the effects of supplementation of individual antioxidants or combinations of antioxidant supplements with chemotherapy in a variety of patient populations. Yet, no cohesive review of these results has been published.

To learn about the relationship between antioxidants and chemotherapy, we conducted a systematic review of the published trials and observational studies investigating: (1) The effects of conventional chemotherapy with or without radiation on antioxidant status; (2) the effects of antioxidant status on treatment-related toxicities and event-free survival; (3) the effects of antioxidant supplementation in combination with conventional chemotherapy with or without radiation on antioxidant status; and (4) the effects of antioxidant supplementation on treatment-related toxicities and event-free survival.

METHODS

Epidemiologic and clinical studies included in this review were identified through repeated literature searches conducted from July 2000 to January 2002. The MEDLINE and Cochrane database was searched for published manuscripts. The reference terms "antioxidants," "supplements," "vitamins," "diet," "nutrition," "cancer," "chemotherapy," "chemotherapy toxicity," and "cancer survival" were used as both keyword and subject terms. In the MEDLINE database, the search was limited to human studies published in English. In addition, journal manuscripts cited in the primary-search manuscripts were collected and added to the review. Data were extracted from the manuscripts using a standardized methodology [14,15]. We included only studies that investigated antioxidant levels and/or antioxidant supplementation in patients receiving chemotherapy with or without radiation therapy for cancer. Studies investigating antioxidant levels in patients with cancer at diagnosis only, after cancer therapy, receiving only radiation therapy, or not receiving cancer therapy, were excluded. Studies investigating other nutrients (nutritional supplements, herbal preparations) with antioxidant capacity, but not defined in the dietary reference intakes as being required from the diet were not included in this review. Studies that reported assessment of vitamins C, E, selenium, or β-carotene as either the primary or a secondary aim were included.

RESULTS

Observational Studies

Table 1 describes 31 observational studies reporting changes in serum, plasma, or whole blood levels of vitamins C and E, selenium, β-carotene, and total radical antioxidant parameter (TRAP), which represents total body antioxidant status, in patients undergoing anticancer therapy. Information is grouped by malignancy and includes subject demographics, cancer data, cancer treatment, end points evaluated, results, and comments. No specific treatment was consistently associated with changes in the individual antioxidants (Table 1).

Three studies reported that TRAP levels decreased after chemotherapy [16-18]. However, the sample sizes in all three studies were small (39, 24, and 12 patients, respectively). In two of the studies, the patients were undergoing high-dose chemotherapy before bone-marrow transplant [16,17]; in the third study, the patients were undergoing therapy for lung cancer [18].

Hematologic malignancies. Twelve observational studies (nine case-control and three cohort) reported on antioxidant status in patients with hematologic malignancies; sample sizes ranged from 13 to 269 subjects. Only eight studies described the anticancer agents administered to patients, and the eight protocols varied. Three studies suggested that after initiation of treatment, vitamin C levels may increase [16,17,19]; one found that plasma ascorbic acid concentrations decreased [20], and one reported that plasma ascorbic acid decreased while dehydroascorbic acid increased [21]. Six studies reported low vitamin E levels in patients receiving high-dose chemotherapy before a bone marrow transplant [16,17,22-25], but the largest study (n = 269) found no change in vitamin E [25]. However, the treatments and the timing of blood sampling in relation to treatment varied. This was also observed in studies assessing β-carotene and selenium levels [22-24,26-28].

Breast cancer. Four studies investigated antioxidant status in patients with breast cancer undergoing cancer therapy. Potischman et al [29] suggested that vitamin E, as measured by α-tocopherol and γ-tocopherol, increased with the initiation of chemotherapy, but this finding coincided with an increase in energy intake; however, another study found the opposite [30]. A third study reported that vitamin E levels increased with the initiation of tamoxifen [31], whereas a fourth study found no significant changes [32].

Lung, gynecologic, and testicular cancer. Five studies investigated subjects with lung [18], gynecologic [33,34], and testicular cancers [35,36]. Different end points, therapies, stages of malignancy, and timing of blood withdrawal preclude any systematic comparisons.

Heterogeneous cancers. Ten observational studies investigated antioxidant status in subjects with a range of malignancies (both hematologic and solid) and compared subjects treated on varying protocols and with different classes of anticancer agents [33,37-46]. Sample sizes varied (range, N = 14 to N = 802), and the timing of blood withdrawal ranged from diagnosis to hours, days, or months after initiation of treatment. No trends among these studies were observed.

Table 1. Observational Studies

Study	Groups and Demographics	Malignancies	Treatments	Antioxidants	Results	*Strengths*/Weaknesses
Hematologic malignancies						
Durken et al [16]	High-dose chemotx: n = 38, mean age: 42.5 y; TBI + chemotx: n = 8, mean age: 39 y; controls: n = 23, mean age: 39 y, age range: 20–56 y	AML, ALL, NHL, PV	BU, VP16, CY, TBI	Plasma TRAP, VC, α-Toc	In high-dose chemotx: TRAP day −8 > day 0 ($P < .02$), TRAP ↑ with VP16 ($P < .02$), VC day −8/−7 < day +14; In TBI + chemotx: TRAP day −7 > day 0 ($P < .02$), day 0 < day 14 ($P = .02$), VC day −8/−7 < day 14	*Timing of specimen collection reported*
Durken et al [17]	Patients: n = 7, median age: 34 y; controls: n = 17, median age: 30 y	AML, CML, MM	BU, VP16, CY	Plasma TRAP, VE, VC	TRAP ↓ during chemotx ($P < .05$), VC ↑ during chemotx ($P < .05$)	*Similar treatment regimens; Timing of specimen collection consistent*
Nakagawa et al [19]	Patients at baseline: n = 57, mean age: 9.7 y; post-chemotx: n = 16, mean age: 8.7 y; controls: n = 31, mean age: 48 y	ALL	NR	AsA and ASR in serum and CSF	CSF > serum but correlated in all three groups, patients AsA > controls	CSF AsA and ASR uninterpretable; follow-up specimens obtained for only 16/57 patients; adult controls for pediatric patients
Kakar et al [20]	Patients: n = 10, age range: 4–14 y; controls: n = 10, age range: 4–14 y	ALL	PRED, VCR, 6-MP	Plasma and leukocyte AA	AA in patients < controls	*Dietary intake assessed*/ no data on disease stages, time since dx, specific chemotherapy regimens, timepoints of assessments
Abou-Seif et al [21]	Patients: n = 17, controls: n = 10	ALL, NHL, HD	VCR, PRED, END, ADR	Plasma AsA and DasA	AsA ↓ postchemotx, DasA ↑ during chemotx ($P < .001$)	No data on demographics or timing of specimen collection
Clemens et al [22]	Patients: n = 19, median age: 23 y; TBI + *v* TBI-	AL, MDS, CGL, NB, SAA	CY, TBI, VP16, MELPH	Plasma α-Toc/chol and β-Car/chol	α-Toc/chol molar ratio ↓ during chemotx ($P < .001$) TBI+ β-Car/chol ↑ during chemotx and < TBI ($P < .005$)	No stratification on conditioning regimens; same sample as ref. 23
Clemens et al [23]	Patients: n = 19, median age: 23 y	AML, NB, SAA, CGL, MDS, ALL	CY, TBI, VP16, MELPH	Plasma and RBC α-Toc, plasma β-Car	α-Toc ↓ 29% day − 8 to day 0 ($P < .01$), αToc/chol ↓ 28% day 0 to day +12 ($P < .01$), RBC membrane α-Toc ↓	No stratification for conditioning regimens; same sample as ref 22
Ladner et al [24]	Patients: n = 13	AL, SAA, MDS, CGL	CY, VP16	Plasma and RBC α-Toc, plasma β-Car	Postchemotx ↓ in α-Toc/chol ratio ($P = .01$), RBC α-Toc ($P < .0001$), β-Car/chol ratio ($P = .02$)	Subset of sample in refs 22 and 23
Marco et al [25]	Patients: n = 182, age range: 17–86 y; controls: n = 87, age range: 20–64 y	ALL, ANLL, MM, CLL, CML, HD, NHL	NR	Serum α-Toc	No significant findings	No stratification on type of hematologic malignancy, treatment, age, time since diagnosis
Calautti et al [26]	Patients: n = 88, age range: 11–78 y; controls: n = 34, age range: 20–56 y	NHL, HD, CLL	Chemotx, RT	Serum Se	Se in CLL at dx < controls	No stratification on lymphomas, treatments, age groups; selective follow-up
Pazirandeh et al [27]	Patients: n = 60, age range: 3–8 y; controls: n = 80	AML, ALL	Hormones, antimetabolites, antibiotics, vegetable alkaloids	Serum Se	Se in ALL postinduction < baseline ($P < .001$), Se in AML baseline < controls ($P < .02$)	No data on specific treatments; little demographic data; no data on ages of controls
Beguin et al [28]	Patients: n = 70, mean age: 49 y	ANLL	DNR, VCR, CAR, VP16, DHAD, AMSA, MELPH	Serum Se	Prechemotx patients' SE < controls	

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Table 1. Observational Studies (continued)

Study	Groups and Demographics	Malignancies	Treatments	Antioxidants	Results	*Strengths*/Weaknesses
Breast cancer						
Potischman et al [29]	Patients: n = 71; controls: n = 95	Breast	No chemotx, chemotx, TAM	Plasma α-Toc, γ-Toc, β-Car at baseline and 3–4 months	Controls: γ-Toc ↑ (P = .006); no chemotx: β-Car ↑ (P = .003); chemotx: α-Toc ↑ (P = .02), γ-Toc ↑ (P = .001); TAM: α-Toc ↑ (P = .002)	*Subjects completed diet history*/no data on specific treatment regimens; no stratification on stage
Subramaniam et al [30]	Patients: n = 55; controls: n = 24	Breast	CY, MTX, FU	Serum AA, VE, Se	Postchemotx ↓ in AA (P < .05), VE (P < .001), Se (P < .001)	*Blood collected after overnight fast*/no mention of informed consent; no demographic data
Thangaraju et al [31]	Patients: n = 64	Resectable, breast	TAM	Serum VC, VE, Se	6 months postchemotx ↑ in Se (P < .05), VC (P < .05), VE (P < .01)	No healthy controls; no demographic data
Vernie et al [32]	Patients: n = 7, mean age: 48 y Controls: 7, mean age: 48 y	Breast	MTX, FU, CY, RT	Serum, whole blood, and erythrocyte Se	No significant findings	No mention of informed consent; no stratification on stage; specimens not obtained at consistent time intervals
Lung cancer						
Erhola et al [18]	Patients: n = 12, mean age: 60 y	SCLC	VCR, ADR, CY	Plasma TRAP, VC, VE	TRAP ↓ 8 hr after chemotx (P = .03), VC ↓ 20 hr after chemotx (P = .04)	*Single diagnosis; data collected on vitamin intake*/no stratification on treatment or smoking status
Gynecologic cancers						
Sundstrom et al [33]	Patients: n = 40, mean age: 57 y; controls: n = 40, mean age: 57 y	Ovarian	FTO, CIS, DXR, CY, RT	Serum Se	Prechemotx patients < controls (P < .01), Postchemotx ↑ with CR, ↓ with poor prognosis (P = .002)	No stratification on stage or regimen; specimens not obtained at consistent time intervals
Bhuvaraha murthy et al [34]	Patients: n = 235, mean age: 45 y; controls: 100, mean age: 46 y	Uterine, cervical	CIS, RT, CY	Serum VC, α-Toc, Se	Stage III patients' α-Toc and Se ↑ post chemotx (P < .05)	*Results stratified by cancer stage*
Testicular cancer						
Vernie et al [35]	Patients: n = 15, mean age: 30 y	Metastatic testicular	CIS, VBL, BLEO	Plasma and RBC Se	No significant findings	
Atukorala et al [36]	Patients: n = 14, mean age: 27 y; controls: n = 8, mean age: 24 y	Metastatic testicular teratoma	Cis-DDP, BLEO, VBL	Plasma VC and VE	Prechemotx VC < controls, VE ↓ during 1st (P < .001) and 2nd (P < .01) courses	Antioxidant levels assessed during consecutive courses of chemotx
Heterogeneous cancers						
Koskelo et al [37]	Patients: n = 24, age range: 1–13 y controls: n = 89 age: 5 y	ALL, ANLL, Hist, Wilms, OS, RB, Askin, NB	Unspecified	Serum Se	Baseline Se in solid tumors > leukemia (P = .001); leukemia Se ↑ during chemotx	*Stratified by type of malignancy*/no data on treatment regimens
Bratakos et al [38]	Patients: n = 177, mean age: 56 y	Unspecified	Unspecified	Whole blood, urine, hair, tissue, Se	Patient blood, urine, hair Se < controls (P < .01); breast cancer patient blood and hair Se < controls (P < .01); hematologic cancer patient blood, urine, hair Se > controls (P < .01)	No data on types of malignancies or treatment; subjects included children and adults
Weijl et al [39]	Patients: n = 36, mean age: 37 y (male) mean age: 43 y (female)	OS, testicular, H/N, GI, Hist	Unspecified	Plasma VC, VE, β-Car, Se	Postchemotx VC and VE ↓ (P < .001)	*Collected dietary data and anthropometric measures*/no stratification by malignancy

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Table 1. Observational Studies (continued)

Study	Groups and Demographics	Malignancies	Treatments	Antioxidants	Results	*Strengths*/Weaknesses
Faber et al [40]	Patients: n = 15, age range: 23–66 y; Controls: n = 20	Breast, lung, cavum, testicle, myosarcoma, uterine sarcoma	ADR, VP16, CY, 5-FU, IFOS	Plasma VE, β-Car, Se	Prechemotx Se < controls ($P < .05$); postchemotx VE ↓ ($P < .005$)	No stratification by malignancy
Malvy et al [41]	Patients: n = 170, age range: 0–6 y; Controls: n = 632	Mixed, unspecified	Unspecified	Serum α-Toc, β-Car	Prechemotx patients' α-Toc and β-Car > controls ($P < .001$); Postchemotx bone cancer patients α-Toc < controls ($P < .001$)	No stratification by malignancy; no data on treatment regimens
Faure et al [42]	Patients: n = 14, age range: 23–73 y	Mixed, unspecified	ADR, IFOS, VCR, Dexa, MTX, CIS	Plasma α-Toc, β-Car	α-Toc ↓ during chemotx ($P < .05$)	No stratification by malignancy
Schreurs et al [43]	Uterine cancer: n = 28, mean age: 63 y, bladder prostate: n = 50 (male) mean age: 69 y NHL/HD: n = 24, mean age: 43 y; controls: n = 130	Uterine, bladder, prostate, NHL, HD	Chemotx unspecified	Serum VC and VE prechemotx, 4 weeks, 19 weeks	Uterine VE and VC ↓ at 4 weeks ($P < .01$), ↑ at 19 weeks ($P < .01$); bladder/prostate VE ↑ at 19 weeks ($P < .01$); NHL/HD VE ↑ at 4 and 19 weeks ($P < .01$)	
Broghamer et al [44]	Patients: n = 10; controls: n = 52	Pulmonary, H/N, GI, GU	Unspecified	Serum Se	Patient Se < controls ($P < .02$), ↓ Se correlated with recurrence ($P < .05$), multiple primaries ($P < .001$), mortality ($P < .001$)	
Broghamer et al [45]	Patients: n = 110; controls: n = 52	Pulmonary, H/N, GI, GU	Unspecified	Serum Se	Patient Se < controls ($P < .02$), ↓ Se correlated with recurrence ($P < .05$), multiple primaries ($P < .001$), mortality ($P < .001$)	No stratification by malignancy
Robinson et al [46]	Patients: n = 146, age range: 16–65 y; controls: n = 104, age range: 30–90 y	Unspecified	Unspecified	Blood Se	No significant findings	No stratification

Abbreviations: y, years; HD, Hodgkin's disease; Chemotx, chemotherapy; TBI, total body irradiation; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; PV, polycythemia vera; CML, chromic myelocytic leukemia; MM, multiple myeloma; AL, acute leukemia; MDS, myelodysplastic syndrome; CGL, chronic granulocytic leukemia; NB, neuroblastoma; SAA, severa aplastic anemia; BU, busulfan; VP 6, etoposide; CY, cyclophosphamide; NR, not reported; PRED, prednisone; VCR, vincristine; 6-MP, 6-mercaptopurine; END, endoxane; ADR, adriamycin; MELPH, melphalan; TRAP, total radical antioxidant parameter; VC, vitamin C; α-Toc, alpha tocopherol; γ-Toc, gamma tocopherol; VE, vitamin E; AsA, ascorbate; ASR, ascorbyl radical; AA, ascorbic acid; DasA, dehydroascorbic acid; Chol, cholesterol; β-Car, beta carotene; ANLL, acute non-lymphocytic leukemia; CLL, chronic lymphocytic leukemia; RT, radiation therapy; DNR, daunorubicin; CAR, cytarabine; DHAD, mitoxantrone; AMSA, amsacrine; Se, selenium; ↓, decrease; ↑, increase; dx, diagnosis; SCLC, small-cell lung cancer; TAM, tamoxifen; MTX, methotrexate; FU, fluorouracil; FTO, ftorafure; CIS, cisplatin; DXR, doxorubicin; CR, complete remission; Hist, histiocytosis; OS, osteosarcoma; RB, rhabdomyosarcoma; NB, neuroblastoma; H/N, head and neck cancer; GI, gastrointestinal cancer; GU, genitourinary cancer; IFOS, ifosfamide; Dexa, dexamethasone; hr, hours.

Clinical Trials

Effects of supplementation on blood antioxidant levels. Table 2 describes nine trials in which the effects of various supplements on plasma, serum, and/or platelet antioxidant levels were assessed. These studies are grouped by malignancy and describe subjects, diagnosis, cancer therapy, dosage and mode of antioxidant supplementation, end points evaluated, results, and comments.

Hematologic malignancies. Five studies were performed in patients with hematologic malignancies [22,47-50]. In the four studies that included oral or intravenous vitamin C alone or in combination with other vitamins, no clear trends emerged [47-50]. Only one study investigated the independent effect of vitamin C [50]. Patients with acute leukemia or chronic myelogenous leukemia who received vitamin C supplements had significant increases in platelet and plasma levels of vitamin C ($P < .025$, $P < .025$, respectively); patients with chronic lymphocytic leukemia experienced a significant increase in plasma vitamin C levels ($P < .05$).

Three of the five studies in patients with hematologic malignancies investigated the effects of vitamin E supplementation in combination with other nutrients on plasma vitamin E, α-tocopherol/RBC membranes ratio, α-tocopherol/cholesterol ratio, or serum vitamin E [22,47,48].

Table 2. Clinical Trials (variables observed: vitamins C, E, selenium, and β-carotene, ORAC)

Study	Sample Size and Demographics	Cancer Agents	Dosage and Mode	Study Design	Results	*Strengths*/Weaknesses
Hematologic malignancies						
Clemens et al [22]	Subjects: n = 19	CY, MEL, VP16, TBI	α-Toc 9 mg (TPN)	Cohort study	Subjects (TBI+): serum α-Toc and β-Car ↓ (baseline *v* day +12); TBI− α-Toc over time ($P < .001$), no significant changes in β-Car	Significant differences between two groups at baseline; nonrandomized, small cohort, no controls; intervention assessed the effects of RDA only
Clemens et al [47]	Subjects: (TBI+) n = 16, mean age: 30.5 y; Controls: (TBI−) n = 10, mean age: 37.5 y	CY, VP16, BU, TBI	TBI+: α-Toc 825 mg, β-Car 45 mg, AA 450 mg, (PO); TBI−: AA 530 mg, α-Toc 9 mg (TPN)	Nonrandomized, nonblinded, controlled trial	↓ Hepatotoxicity; no significant differences in rates of relapse	Study groups received different TPN regimens; significant differences were not observed at each timepoint; *P* values NR; small cohort, different anticancer regimens; TBI+ also received 130 mg AA and 13.1 mg α-Toc by TPN
Hunnisett et al [48]	Controls: n = 19, mean age: 33 y; Subjects: n = 10, mean age: 37 y	High-dose chemotx, +/− TBI	VC 25 mg; VE 1,000 IU (TPN)	20 sequential patients	Acute ↓ in VC and VE ($P < .001$; $P < .001$); no significant differences after day 0	Nonrandomized, small cohort; cancer diagnosis and agents NR
Jonas et al [49]	Standard TPN: n = 11, mean age: 41 y; Modified TPN: n = 13, mean age: 38 y	BU, CY, DZ, TP, Ara-C, TBI	Modified TPN: kCal from lipids only; both groups: AA 500 mg (TPN)	Double-blind, randomized trial	No significant differences in pre- *v* day 1 postchemotherapy; α-Toc ↑ at baseline v day 14 in entire cohort ($P < .05$); decline more pronounced in standard TPN ($P < .05$); γ-Toc ↓ over time ($P < .001$), plasma AA ↑ over time ($P < .01$)	*Well-designed trial; observed acute and long-term effects*/ standard TPN group received 700 mg AA
Lloyd et al [50]	Controls: n = 26, age range: 18–28 y; subjects: n = 16, intervention: n = 6	NR	AA 1 g × 4 days (mode NR)	Cohort study	Prior to intervention: mean platelet and plasma AA ↓ in CML controls ($P < .001$; $P < .05$), mean platelet AA ↓ in CML *v* controls ($P < .05$); after intervention: ↑ in platelet and plasma AA in AL & CML ($P < .025$) ↑ plasma AA in CLL ($P < .05$)	*Inquired about dietary intake*/ Cancer therapy NR; time of blood withdrawal, length of observation, and timing of intervention NR; methodology NR
Lung cancer						
Jaakola et al [51]	Subjects: n = 18, age range: 51.8 - 69.6 y	CY, ADR, VP16, VCR, DXR, EPI CBPT, RT	MV+ β-Car 10,000–20,000 U, α-Toc 300–800 U, AA 2000–5000 U, Se 856 μg (PO)	Nonrandomized controlled trial	Study group had increased survival rates compared to historical controls (*P* value NR); plasma Se, α-Toc NS, plasma AA, β-Car NR	Variable doses administered depending on "individual" micronutrient analysis (methodology NR); multiple stages combined; one subject received no cancer therapy
Gynecologic cancer						
Sundstrom et al [52]	Subjects: n = 56; controls: n = 44, mean age: 58.7 y	DXR, CY, CDDP, MELPH	Four arms: 1) VE 300 mg, Se 96 μg; 2) Se 96 μg; 3) VE 300 mg; 4) placebo (PO)	Controlled trial	↑ in serum Se in Se group 1 and group 2 *v* controls ($P < .001$; $P < .001$)	Placebo controlled trial/multiple gynecologic cancers, stages, and regimens
Sundstrom et al [52]	Subjects: n = 29; controls: n = 12, mean age: 57.4 y	DXR, CY, CDDP, MELPH	Four arms: 1) VE 300 mg, Se 200 μg; 2) Se 200 μg; 3) VE 300 mg; 4) placebo (PO?)	Controlled trial	Group 1: serum Se ↑ at 4 weeks and 8 weeks *v* baseline ($P < .001$; $P < .001$); group 2: serum Se ↑ at 4 weeks and 8 weeks ($P < .001$; $P < .001$); group 3: NS	Placebo controlled trial/small cohort, multiple diagnoses, stages, and regimens; mode of administration not clearly reported; serum VE NR
Breast cancer						
Lockwood et al [54]	Subjects: n = 32, age range: 32–81 y	Chemotx, RT, Surgery	VC 2,850 mg, VE 2,500 IU, β-Car 32,500 U, Se 387 μg (PO)	Nonrandomized, noncontrolled trial	Whole blood β-Car, VE, and Se ↑ after 3 and 12 months ($P < .01$), $P < .05$), $P < .01$); no deaths, expected four; no subject had weight loss, ↓ use of pain killers, ↑ QOL	Whole blood VC NR, no controls, chemotherapy agents NR; subjects also administered MV containing Co-Q10 and essential fatty acids; *P* values not consistently reported

Abbreviations: ORAC, Oxygen radical absorbance capacity; CY, cyclophosphamide; MELPH, melphalan; VP16, etoposide; ↓, decrease; ↑, increase; TBI, total body irradiation; α-Toc, alpha tocopherol; TPN, total parenteral nutrition; β-Car, beta carotene; RDA, recommended dietary allowances; y, years; BU, busulfan: PO, orally; AA, ascorbic acid; NR, not reported; VC, vitamin C; VE, vitamin E; DZ, diaziquone; TP, thiotepa; Ara-C, cytosine arabinoside; k-Cal, total caloric intake; CML, chronic myelocytic leukemia; AL, acute leukemia; CLL, chronic lymphocytic leukemia; VCR, vincristine; DXR, doxorubicin; EPI, epirubicin; CBPT, carboplatin; RT, radiation therapy; MV, multivitamin; NS, nonsignificant; CDDP, cisplatinum diammine dichloride; Se, selenium; chemotx, chemotherapy; QOL, quality of life; Co-Q10, coenzyme Q 10; γ-TOC, gamma tocopherol.

Among patients receiving intensive conditioning chemotherapy in the setting of bone marrow transplant (especially those receiving concomitant total-body irradiation), serum vitamin E levels decreased even among patients receiving the recommended dietary allowances of vitamins by total parenteral nutrition [22,49]. Low-dose vitamin E (9 mg) supplementation through total parenteral nutrition did not prevent a decrease in one study [22], and supplementation with 1,000 U of vitamin E combined with low-dose vitamin C (25 mg) had no effect on serum vitamin E or plasma vitamin C levels in another trial [48]. However, another study demonstrated that supplementation with α-tocopherol (825 mg), β-carotene (45 mg), and vitamin C (450 mg) by mouth prevented a decline in plasma antioxidant levels [47].

Lung cancer. One nonrandomized trial was undertaken in patients with lung cancer [51]. Antioxidant supplementation (10,000 to 12,000 U β-carotene, 300 to 800 U α-tocopherol, 2,000 to 5,000 U ascorbic acid, 856 μg selenium) resulted in no significant changes in plasma selenium or α-tocopherol.

Gynecologic malignancies. In two randomized trials [52,53] among patients with gynecologic cancers, patients were treated with doxorubicin, cyclophosphamide, cisplatin with ftorafure or melphalan, and the supplements: selenium (96 μg or 200 μg), vitamin E (300 mg), selenium and vitamin E, or placebo. Both studies reported significantly increased levels of serum selenium but not vitamin E after the initiation of supplementation.

Breast cancer. In a study evaluating patients with breast cancer [54] supplemented with selenium (387 μg) in combination with vitamin C (2,850 mg), vitamin E (2,500 U), β-carotene (32,500 U), coenzyme Q-10, essential fatty acids, and other vitamin and minerals, increases in whole blood β-carotene ($P < .01$), vitamin E ($P < .05$), and selenium ($P < .01$) were observed 3 and 12 months after the start of supplementation.

Taken together, the intervention trials suggest a direct effect of selenium supplementation on serum or whole blood selenium concentrations, despite the variations in malignancies, regimens, and stages of cancer among the patients studied.

Effects of supplementation on chemotherapy-related toxicities. Table 3 describes the results of 12 trials investigating the effects of antioxidant supplementation on chemotherapy-related toxicities. Three studies specifically evaluated the effects of supplementation on common toxicities associated with chemotherapy including nausea/vomiting, fatigue, bone marrow suppression, and diarrhea [55-57]. In patients with ovarian cancer treated with cisplatin and cyclophosphamide, patients who received 3 months of selenium supplementation had significantly higher ($P < .05$) neutrophil counts (but not other hematologic indices) and less nausea/vomiting, abdominal pain, weakness, malaise, and anorexia than controls [55]. Selenium administration reduced cisplatin-induced nephrotoxicity in the acute stages (24 to 48 hours), but not over long-term (> 72 hours) [56]. A phase I trial of fluorouracil, leucovorin, and high-dose vitamin E (3,200 U) among nine patients with advanced disease showed no benefit (partial or complete response) and no reduction or increase in toxicity [57].

Four trials investigated the effects of antioxidant supplementation (vitamin E alone or as part of a combination therapy) on cardiac toxicity in patients receiving anthracycline-based therapy [54-57]. One study found that vitamin E with nifedipine prevented a decrease in left ventricular ejection fraction, especially in the setting of adjuvant radiotherapy, and accelerated the distribution and elimination of doxorubicin ($P < .05$) [58]. The other studies found no effect [59-61]. Antioxidant supplementation had no significant effect on mucositis [62,63], alopecia [64], or skin ulcerations [65].

Effects of supplementation on survival and recurrence. Six studies investigated the effect of antioxidant supplementation on recurrence rates and survival (Table 3) [47,51,54,61,62,66]. Three studies found no effect on recurrence or survival [47,61,62]; two reported a survival benefit with supplementation [51,54], and one study reported significant findings in the short-term (year 1), but not on overall survival [66].

DISCUSSION

Our review of the observational studies of the effects of chemotherapy on antioxidant levels supports the hypothesis that chemotherapy lowers total antioxidant status, but this was assessed in a limited number of studies [16-18]. Studies of changes in vitamins C and E, selenium, and β-carotene found no consistent patterns associated with chemotherapy [16-32,34-46,52]. Based on these studies, we can only conclude that the effect of chemotherapy on levels of the antioxidants assessed is not great enough to have overridden differences in study methodologies, patient populations, cancer organ or site, conventional chemotherapy treatment, and timing of data collection in relation to the natural history of the cancer and its treatment.

An explanation for the lack of consistent change in antioxidant status after chemotherapy treatment may be that patients were depleted of antioxidants before initiation of treatment, perhaps because cancer cells use antioxidant vitamins more efficiently than healthy cells, thus depleting circulating plasma levels of antioxidants. This hypothesis is supported by the studies that found that cancer patients had lower levels of antioxidants than controls, even before the initiation of treatment [9,13,38,44,45,67]. These observations suggest that low antioxidant status may be associated with neoplastic activity and subsequent poor health and support the idea that antioxidant supplementation could benefit cancer patients.

Table 3. Clinical Trials (variables observed: therapy-related toxicities and/or survival/response)

Study	Sample Size and Demographics	Cancer Agents	Dosage and Mode	Study Design	Results	*Strengths*/Weaknesses
General toxicities						
Sieja et al [55]	Treatment group: n = 31, mean age: 49.4 y; controls: n = 31, mean age: 52.7 y	CIS, CY	Se 50 μg, VC 200 mg, VE 36 mg, β-Car 15 mg (PO)	Placebo-controlled trial	$\uparrow$ neutrophil count and % after 12 weeks in treatment group *v* controls ($P < .05$) $\downarrow$ in severity of side-effects in treatment group *v* controls after 12 weeks ($P < .05$)	No randomization or blinding
Hu et al [56]	Patients: n = 41, age range: 31–74 y	CIS-based therapy	Se 4,000 μg (PO)	Crossover trial	Peripheral WBC $\uparrow$ during treatment on days 7 ($P < .05$), 10 ($P < .05$), and 14 ($P < .05$); $\downarrow$ need of blood transfusions and GCSF due to leucopenia in during treatment ($P < .05$, $P < .05$)	Multiple malignancies; anticancer regimens NR
Blanke et al [57]	Patients: n = 9, median age: 50.5 y	FU, LCV	*dl*-α-Toc 3,200 IU (PO)	Phase I trial	No patient had CR or PR; no effect on chemotherapy toxicity	No controls; small cohort; subjects had different histories of cancer therapy
Cardioprotection						
Lenzhofer et al [58]	Subjects: n = 6, age: 59.8 y; controls: n = 6 age: 53 y	DXR	α-Toc 200 mg (IM)	Controlled clinical trial	After 6 hrs of DXR, $\uparrow$ in PEPI:LVETI ratio in controls ($P < .001$); DXR distributed and eliminated faster in subjects ($P < .05$); in controls, correlation between change in PEPI:LVETI ratio and DXR concentration ($P < .001$)	Study also administered nifedipine
Weitzman et al [59]	Subjects: n = 7, mean age: 55 y; controls: n = 9, mean age: 56 y	ADR, VCR, BLEO, FU, MIT, PRC, MTX, RT	*dl*-α-Toc 1,800 U	Randomized, controlled trial	No significant findings	Multiple maligancies and regimens; small cohort; mode of administration unclear; natural α-Toc administered
Wagdi et al [60]	Subjects: n = 25	ADR, CY, BLEO, VCR, PRC, PRED, DAC, VBL, VP16, RT	VC 1g, VE 600 mg,	Double-blind, randomized, placebo-controlled trial	No significant findings	Supplementation also controlled N-acetylcysteine; mode of administration not clearly reported
Legha et al [61]	Subjects: n = 21, mean age: 50 y	FU, ADR, CY	α-Toc 2 gm/m^2 (PO)	Nonrandomized, noncontrolled trial	No significant findings	No controls, randomization, blinding; small cohort; study did not control for cummulative dose of anthracycline therapy
Mucositis						
Mills et al [62]	Subjects: n = 10, controls: n = 10, mean age: 57 y	BLEO, VCR, LCV, MTX, RT	β-Car 250 mg (PO)	Randomized, controlled trial	Subjects had $\downarrow$ in severe mucositis (grade III or IV) ($P < .025$); no significant differences in rates of remission in subjects *v* controls	Multiple regimens and agents; small cohort
Wadleigh et al [63]	Subjects: n = 9, controls: n = 9, mean age: 61 y	FU, CIS, DXR, Ara-C	VE oil 400 mg (topical)	Double-blind, randomized, placebo-controlled trial	Resolution of mucositis was shorter in subjects *v* controls ($P = .025$)	Multiple regimens and diagnosis; small cohort
Alopecia						
Perez et al [64]	Subjects: n = 20, mean age: 53 y	DXR, VCR, FU, CY, CIS	α-Toc 1,600 IU (PO)	Nonrandomized, noncontrolled trial	No significant findings	*DOX dosage within a narrow range in subjects (50–60 mg/m^2)*

(continued on following page)

Table 3. Clinical Trials (variables observed: therapy-related toxicities and/or survival/response) (continued)

Study	Sample Size and Demographics	Cancer Agents	Dosage and Mode	Study Design	Results	*Strengths*/Weaknesses
Skin ulcerations						
Ludwig et al [65]	Subjects: n = 8	MIT, DXR, 4-deoxy DXR	Dressing: α-Toc 90%, DMSO/10% (topical)	Nonrandomized, noncontrolled trial	No significant findings	Concentration of α-Toc NR; confounded by application of DMSO, *P* values NR
Other						
Lamm et al [66]	Subjects: n = 35, mean age: 65.9 y; controls: n = 30, mean age: 68.1 y	Immunotherapy	Subjects: VC 2,000 mg, VE 400 U, MV; controls: MV only	Randomized, controlled trial	No significant difference in rates of recurrence at 10 months; ↓ in recurrences in subjects *v* controls at year 1 ($P < .008$); ↓ in 5-year estimates of recurrence in subjects *v* controls ($P = .0014$); ↓ in overall recurrence in subjects controls ($P < .011$); ↓ in patients with more than two or more episodes of recurrence in subjects *v* controls ($P < .0375$); overall survival NS	*Study investigated short and long-term effects of supplementation*/administration of MV may have confounded results; did not control for lifestyle during the observation period

Abbreviations: y, years; CIS, cisplatin; CY, cyclophosphamide; VC, vitamin C; VE, vitamin E; β-Car, beta carotene; PO, orally; GCSF, granulocyte colony stimulating factor; FU, fluorouracil; LCV, leucovorin; α-Toc, alpha-tocopherol; CR, complete remission; PR, partial remission; DXR, doxorubicin; IM, intramuscular; PEPI: LVETI, pre-ejection period–left ventricular ejection time; ADR, adriamycin; VCR, vincristine; BLEO, bleomycin; MIT, mitomycin; PRC, procarbazine; MTX, methotrexate; RT, radiotherapy; PRED, prednisone; DAC, dacarbazine; VBL, vinblastine; VP16, etoposide; Ara-C, cytosine arabinoside; DOX, doxorubicin; DMSO, dimethylsulfoxide; NR, not reported; MV, multivitamin; NS, nonsignificant.

The initiation of anticancer therapy may also lower levels of antioxidants by affecting dietary intake, but as treatment progresses and the cancer cell burden declines, antioxidant levels may improve. Different agents, in the setting of different cancers and stages may also vary in their effects on antioxidant levels [16,17,29,34,37]. However, the finding that TRAP (a measure of total antioxidant capacity) levels consistently decreased, while the individual antioxidants showed no consistent changes, suggests that factors other than known antioxidants may contribute to changes in the total antioxidant status of the body during chemotherapy.

The clinical trials suggest that individual antioxidants administered in conjunction with conventional therapy may affect serum values for some nutrients but not others. Selenium supplementation appears to have the most consistent effect on selenium levels in patients undergoing chemotherapy.

The antioxidant most publicized for its potential benefits to cancer patients is vitamin C. The intervention studies in this review supplemented patients with vitamin C orally or as part of total parental nutrition, but doses did not exceed 5,000 mg. None of the studies reported a beneficial effect from vitamin C [68,69]. Double-blind randomized control trials investigating a high-dose regimen failed to find a significant effect [68].

Much of the debate surrounding antioxidants in combination with chemotherapy has centered on regimens that are believed to achieve their cytotoxic effects by generating free radicals, such as alkylating agents, antimetabolites and radiation. The mechanisms of these agents have been extensively reviewed [70]. In theory, antioxidants may decrease the efficacy of these agents by quenching free radicals. Lenzhofer et al [58] found that supplementation with vitamin E altered the metabolism of doxorubicin. However, such interactions may not necessarily reduce treatment efficacy; certain adjunctive agents, such as mesna, exert their effects through the quenching of free radicals and do not appear to decrease the efficacy of chemotherapy. Similarly, amifostine, an agent with antioxidant properties, is utilized to reduce the side effects associated with cisplatin therapy. Individuals treated with anticancer agents that deplete antioxidant status may require replenishment of antioxidants after treatment, just as patients receiving high-dose methotrexate require leucovorin rescue. Antioxidant supplements may reduce the frequency and severity of toxicity associated with anticancer therapy. Antioxidant use might make it possible to administer higher and more effective doses of chemotherapy.

However, the published studies reviewed here do not provide evidence that individual antioxidant vitamin supplements reduces the toxicity associated with anticancer

therapy. Either antioxidants do not reduce toxicity or more potent antioxidants or higher dosages of individual antioxidants may be needed to minimize the side effects of anticancer therapy. Timing may also be important; supplementation may have to be introduced very early in therapy before the cumulative doses reach their peak [58].

Two of the studies reviewed suggested that supplementation with selenium might reduce the hematologic toxicity and nephrotoxicity associated with cisplatin-containing regimens [55,56]. However, follow-up was not long enough for assessment of effects on survival. Moreover, various regimens were studied and the timing of the interventions were not reported clearly. None of the intervention studies reported controlling for dietary intake of antioxidants in a systematic manner, despite consistent findings that dietary intake of foods high in antioxidants alters serum levels [71].

Prospective studies investigating the effects of antioxidant supplementation before diagnosis on breast cancer mortality suggest that high intake of vitamin C may be beneficial [72-75]. Epidemiologic studies in patients with prostate cancer suggest that selenium and vitamin E may reduce the risk of prostate cancer [76]. This review found no effect of antioxidant supplementation during treatment on survival, but the six relevant studies differed in design and exposure and outcome measures. Studies of the effects of antioxidant supplementation on cancer recurrence and survival should specify both dosage and duration of supplementation and lifestyle (diet, exercise, and so on) in a defined population.

A major barrier to the determination of the effects of antioxidants is the variability of doses, timing, and duration of supplementation in the studies reviewed. The recommended dietary allowances (RDA) for vitamins and minerals are commonly applied to patients with cancer, but the RDA is intended to establish a guideline to prevent nutrient deficiencies and promote health in the majority of healthy individuals; they do not necessarily apply to individuals suffering from a chronic illness or individuals under metabolic stress [77]. The RDA may especially be insufficient to maintain plasma antioxidant levels in patients undergoing high-dose chemotherapy before stem-cell transplant.

Additional studies investigating the effects of antioxidants are needed. Ideally, they should be incorporated into large-scale phase III clinical trials in relatively homogeneous patient populations receiving well-specified conventional treatment regimens. These studies should control for behavioral factors, such as use of complementary/alternative medicine, patient compliance, and carcinogen exposure, particularly for those cancers strongly associated with a specific carcinogen such as lung cancer with tobacco use [29]. In such settings, the variability observed in our review of the literature would not obscure the true effect, if any, of antioxidant supplementation.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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