

Use of antioxidant supplements during breast cancer treatment: a comprehensive review

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Abstract *Purpose* An estimated 45–80% of breast cancer patients use antioxidant supplements after diagnosis, and use of antioxidant supplements during breast cancer treatment is common. Dietary supplements with antioxidant effects include vitamins, minerals, phytonutrients, and other natural products. We conducted a comprehensive review of literature on the associations between antioxidant supplement use during breast cancer treatment and patient outcomes. *Methods* Inclusion criteria were: two or more subjects; clinical trial or observational study design; use of antioxidant supplements (vitamin C, vitamin E, antioxidant combinations, multivitamins, glutamine, glutathione, melatonin, or soy isoflavones) during chemotherapy, radiation therapy, and/or hormonal therapy for breast cancer as exposures; treatment toxicities, tumor response, recurrence, or survival as outcomes. *Results* We identified 22 articles that met those criteria. Their findings did not support any conclusions regarding the effects of individual antioxidant supplements during conventional breast cancer treatment on toxicities, tumor response, recurrence, or survival. A few studies suggested that antioxidant supplements might decrease side effects associated with treatment, including vitamin E for hot flashes due to hormonal therapy and

glutamine for oral mucositis during chemotherapy. Underpowered trials suggest that melatonin may enhance tumor response during treatment. *Conclusion* The evidence is currently insufficient to inform clinician and patient guidelines on the use of antioxidant supplements during breast cancer treatment. Thus, well designed clinical trials and observational studies are needed to determine the short- and long-term effects of such agents.

Keywords Breast cancer · Antioxidant supplements · Complementary and alternative medicine · Chemotherapy · Radiation therapy · Hormonal therapy

Introduction

In 2008, approximately 180,000 women will be diagnosed with breast cancer [1], and an estimated 45–80% of these women will use antioxidant supplements after diagnosis, including during breast cancer treatment [2–12]. However, the effects of antioxidant supplements during radiation therapy, chemotherapy, and hormonal therapy on treatment toxicities, tumor response, recurrence, and survival are unknown [13–15], and guidelines regarding the use of antioxidant supplements during cancer treatment are inconsistent [16].

Many forms of chemotherapy and radiation therapy act primarily through oxidative stress pathways [17–19]. The purpose of these treatments is to induce the apoptotic cascade, through mechanisms such as altering DNA replication and disrupting mitochondrial membranes. However, these treatments may also damage healthy tissues, such as the oral mucosa and the heart. Some investigators have hypothesized that antioxidant supplements can provide protection against these treatment toxicities, which can be dose-limiting, can

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cause morbidity, and may contribute to mortality [20–24]. Others have expressed the concern that, like some treatment agents, antioxidant supplements may not differentiate between healthy tissue and tumors; if antioxidant supplements protect healthy tissue, they may simultaneously protect tumor tissue from treatment agents [14, 25]. Still other investigators have suggested that antioxidant supplements may actually potentiate chemotherapy and radiation therapy either by acting as pro-oxidants or by facilitating exposure of the tumor to reactive oxygen species [20, 21]. None of these theories is supported by solid clinical data. A recently published literature review on the use of antioxidants during radiation therapy and chemotherapy for any cancer type concluded that, despite insufficient evidence of harmful effects, antioxidant use should be discouraged due to the possibility that it might protect tumors and reduce survival [13].

An antioxidant supplement can be broadly defined as any dietary supplement that exerts antioxidant actions. Antioxidant supplements can be purchased over the counter individually or in combination with other antioxidants, vitamins, or vitamins and minerals as components of multivitamins. Many cancer patients believe that antioxidant supplements taken during treatment may counteract oxidative damage to healthy tissues, have direct anti-cancer activity, or confer general health benefits. Some supplements used primarily for specific purposes (e.g., soy isoflavones to counter hot flashes, melatonin to enhance immune function, and glutamine to prevent stomatitis) also have general antioxidant actions.

To our knowledge, there are no reviews of the literature on the effects of antioxidant supplementation specifically during breast cancer treatment. This review summarizes the findings of clinical trials and observational studies regarding the effects of antioxidant supplements during breast cancer treatment on treatment-related toxicities, tumor response, recurrence, and survival.

Methods

Observational studies and clinical trials included in this review were identified through repeated literature searches on PubMed conducted July 2006 through October 2007. Combinations of the following reference terms were used as both keywords and subject terms during the searches:

- Cancer site—breast cancer, breast neoplasm;
- Antioxidant supplements—antioxidants, supplements, vitamins, multivitamin, vitamin C, vitamin E, zinc, selenium, beta-carotene, coenzyme Q10, glutathione, *N*-acetyl cysteine, melatonin, soy isoflavones, green tea;
- Treatment—chemotherapy, radiation therapy, hormonal therapy;

- Outcomes—toxicity, oxidative stress, tumor marker, tumor response, recurrence, survival;
- Study design—observational study, epidemiology, clinical trial.

The search was limited to human studies published in English, French, or German. Relevant references listed in primary-search manuscripts were collected and added to the review. In addition, we searched for review articles published on this topic and added relevant cited references to our review.

We included articles that met the following criteria:

- Sample:* including two or more breast cancer patients;
- Design:* clinical (controlled or uncontrolled) trial or observational study;
- Exposure:* documented use of antioxidant supplements during chemotherapy, radiation therapy, or hormonal therapy;
- Outcome:* toxicity, tumor response, recurrence, or survival in treated breast cancer patients.

The supplements that are most commonly considered to be antioxidants are vitamin C, vitamin E, selenium, and zinc. For the purposes of this review, we also included antioxidant combinations, multivitamins, glutamine, glutathione, melatonin, and soy isoflavones because they are also known to have antioxidant activity. Table 1 summarizes the properties and antioxidant actions of each of the dietary supplements that were eventually included in the review.

We limited our search to articles about antioxidant dietary supplements, that is, tablets, capsules, or powders, as opposed to foods or beverages, containing antioxidants. We excluded articles on antioxidant use during hematopoietic stem cell transplant therapy because this treatment has been proven to be no more effective than other less toxic treatment options and is no longer used in clinical practice [26]. We also excluded articles that reported on the prevalence of antioxidant use without reference to relevant clinical outcomes. Only breast cancer-specific outcomes were included for studies that reported outcomes for multiple tumor sites. Articles that provided outcomes for a mix of tumor sites were excluded if they did not provide results specific to subjects with breast cancer.

Results

Our search yielded 19 articles reporting the results of clinical trials and three articles reporting the results of observational studies that met our criteria for inclusion. The 19 articles from clinical trials represented nine randomized controlled trials, four non-randomized controlled trials, and six

Table 1 Antioxidant actions of antioxidant supplements

Antioxidant supplement	Properties and antioxidant actions
Vitamin C (ascorbic acid)	<ul style="list-style-type: none"> • Water soluble. • Synergistic with other antioxidants, but interacts primarily with vitamin E to regenerate active α-tocopherol from α-tocopherol radicals in membranes and lipoproteins. • Protects against lipid peroxidation by scavenging reactive oxygen species in the aqueous phase before they can initiate lipid peroxidation. • Main antioxidant actions include protecting membranes against oxidation and reducing general in vivo oxidative stress. • May also act as a pro-oxidant by releasing metal ions from damaged cells and inducing lipid hydroperoxide decomposition to DNA-reactive bifunctional electrophiles.
Vitamin E (tocopherols)	<ul style="list-style-type: none"> • Lipid soluble. • Exists in eight different forms; in humans, α-tocopherol is the most active form. • Is the primary membrane-bound antioxidant used by cells. • Main function is to protect against lipid peroxidation of poly-unsaturated fatty acids. • After α-tocopherol radicals are produced during the antioxidant reaction, ascorbic acid acts to reduce α-tocopherol to its original form. • The transport and storage of vitamin E depend on selenium, and the absorption of vitamin E is reduced when vitamin A and β-carotene levels are high.
Beta-carotene	<ul style="list-style-type: none"> • Primary precursor for vitamin A (vitamin A is a lipid soluble vitamin, which is not an antioxidant). Two molecules of vitamin A are formed when one molecule of β-carotene is cleaved in half; this reaction requires vitamin E. • Over 600 carotenoids are found as pigments in plants and microorganisms, many of which have antioxidant properties. • Carotenoids act as antioxidants mainly because their conjugated double-bonded structure can delocalize unpaired electrons. • There is some evidence that β-carotene may act as a pro-oxidant. In the ATBC and CARET studies β-carotene supplementation increased risk of lung cancer in male smokers and asbestos workers [55, 56].
Selenium	<ul style="list-style-type: none"> • Trace mineral. • Not an antioxidant, but plays important role in antioxidant seleno-enzymes, including glutathione peroxidases and thioredoxin, which protect DNA and other cellular components from oxidative damage.
Zinc	<ul style="list-style-type: none"> • Trace mineral. • Not an antioxidant, but is required for activity of some antioxidant enzymes.
Coenzyme Q10 (ubiquinone)	<ul style="list-style-type: none"> • Lipid soluble antioxidant. • May protect against mitochondrial ROS. It is synthesized in the mitochondria and in most intracellular membranes, and is ingested via diet and dietary supplements. • CoQ10 plays an integral part in generating intracellular ATP within the mitochondrial inner membrane and in quenching intracellular oxidative stress. • Is specifically hypothesized to protect against anthracycline-induced cardiotoxicity [57].
Glutamine	<ul style="list-style-type: none"> • Most abundant free amino acid in the body. • Precursor to glutathione and plays a major role in regulating the intracellular redox potential. • Acts as a substrate for nucleotide synthesis in dividing cells [58].
Glutathione	<ul style="list-style-type: none"> • Non-essential water soluble tripeptide that exists in reduced (GSH) and oxidized (GSSG) states. • In the reduced state, it acts as an antioxidant by donating electrons to reactive oxygen species. GSH is regenerated from GSSG by the enzyme glutathione reductase. • Protects against general oxidative damage in healthy tissues.
Melatonin	<ul style="list-style-type: none"> • Hormone released by pineal gland. • Is an antioxidant that can easily cross cell membranes and the blood–brain barrier. It is a direct scavenger of OH, O₂⁻, and NO. Unlike other antioxidants, it does not undergo redox cycling. • Has antiproliferative and immunostimulating properties [59].
Soy isoflavones	<ul style="list-style-type: none"> • Extract from soy beans. • Are phytoestrogens. • Among the isoflavones, genistein has the highest antioxidant activity. • Can neutralize free radicals and have been found to decrease lipid peroxidation.

single-arm trials. The three observational studies were retrospective cohort studies. These studies were conducted in 13 countries and published in English between 1980 and 2007. Studies included one article on vitamin C [27], six articles on vitamin E [28–33], five articles on antioxidant combinations [34–38], one article on multivitamins [39], two articles on glutamine [40, 41], one article on glutathione [42], three articles on melatonin [43–45], and three articles on soy isoflavones [46–48]. Sample sizes ranged from 2 to 326 subjects. Table 2 summarizes the 22 articles.

We summarize our findings below by grouping studies with outcomes primarily related to (1) treatment toxicities, or (2) tumor response, recurrence, and survival.

Effects of antioxidant supplements on treatment toxicities

Our literature review yielded 13 studies examining the effects of antioxidant supplements on toxicities caused by chemotherapy, radiation therapy, and tamoxifen therapy. Chemotherapy toxicity studies included endpoints related to cardiotoxicity ($n = 3$), alopecia ($n = 2$), intestinal permeability ($n = 1$), oral mucositis ($n = 1$), and urotoxicity ($n = 1$). One study examined fatigue during radiation therapy, and four studies examined hot flashes during tamoxifen treatment. The antioxidant supplements in these studies included vitamin E ($n = 6$), multivitamins ($n = 1$), glutamine ($n = 2$), glutathione ($n = 1$), and soy isoflavones ($n = 3$).

Vitamin E

Six studies examined the use of vitamin E during breast cancer treatment. Two of the studies examined the use of vitamin E to prevent doxorubicin-induced alopecia, three examined the use of vitamin E to prevent doxorubicin-induced cardiotoxicity, and one study examined the use of vitamin E to treat hot flashes during tamoxifen therapy. The alopecia prevention trials included a non-randomized controlled trial ($n = 25$; 1,600 IU *dl*- α -tocopherol per day) [28] and a single-arm trial ($n = 17$ breast cancer patients, of 20 total patients; 1,600 IU α -tocopherol per day) [29]; neither trial showed any clinically beneficial effect. Similarly, no clinical benefit was suggested by any of the three cardiotoxicity prevention trials (a randomized controlled trial, $n = 6$ breast cancer patients of 16 total patients, of 1,800 IU *dl*- α -tocopherol per day; a single-arm trial, $n = 21$, of 2 g/m² of α -tocopherol per day; and a non-randomized controlled trial, $n = 12$, of 200 mg IM tocopherol before chemotherapy) [30–32]. However, a randomized, placebo-controlled trial ($n = 120$) found that 800 IU per day of vitamin E reduced hot flashes among breast cancer patients, 60% of whom were receiving

tamoxifen therapy [33]. The average magnitude of effect was one less hot flash per day ($P \leq 0.05$).

Multivitamins

One randomized, placebo-controlled, double-blind crossover trial ($n = 40$) examined the effect of supplementation with a Centrum Silver multivitamin during radiation therapy on fatigue [39]. Participants were randomized to take either a multivitamin or placebo when they began their radiation therapy, and were crossed over to the other arm midway through radiation therapy. The trial ended at the end of radiation therapy. At the crossover point, midway through treatment, patients taking the multivitamin reported higher rates of fatigue, compared to those on placebo (25% vs. 0%) ($P = 0.035$). Data on fatigue at completion of radiation therapy were not reported.

Glutamine

Two randomized, placebo-controlled trials examined the effect of glutamine supplementation on gastrointestinal epithelia during chemotherapy. One trial ($n = 326$, 2.5 g per day in a swish and swallow solution) found that glutamine reduced the incidence (38.7% vs. 49.7%; $P = 0.026$) and severity of oral mucositis (1.2% vs. 6.7%; $P = 0.005$) during anthracycline-based chemotherapy [41]. Another trial ($n = 60$, 30 g in water per day) found no effects of glutamine on stomatitis and diarrhea during neoadjuvant chemotherapy [40].

Glutathione

One single-arm trial ($n = 2$ breast cancer patients, of 13 total patients) examined the use of IV glutathione (2.5 g in 100 ml saline before and after cyclophosphamide infusions) to prevent urotoxicity during chemotherapy [42]. No urotoxicity was observed in the two breast cancer patients. The small number of breast cancer patients in this study makes results difficult to interpret.

Soy isoflavones

Three randomized, placebo-controlled trials examined the effect of soy isoflavones on hot flashes in postmenopausal women with a history of breast cancer, some of whom were taking hormonal therapy (tamoxifen or raloxifene) [46–48]. Daily doses used in these three studies varied widely (150 mg of soy isoflavones, $n = 177$; 90 mg of soy isoflavones, $n = 123$; 35 mg of soy isoflavones, $n = 72$). The studies were well designed and none showed an effect of soy intake on the frequency or intensity of hot flashes (all $P > 0.05$).

Table 2 Summary of clinical trials and observational studies of antioxidant supplement use during breast cancer treatment ($n = 22$)

Antioxidant supplement Conventional breast cancer treatment	Study design (n)	Patient characteristics	Antioxidant intervention & concurrent treatment	Main findings
<i>Primary outcomes</i>				
Year author (reference)				
<i>Treatment-related toxicities</i>				
Vitamin E				
Chemotherapy				
<i>Alopecia</i>				
1986 Martin-Jimenez [28]	Non-randomized, controlled trial ($n = 25$)	Twenty-five women with history of mastectomy and positive lymph nodes Thirteen/twenty-five women referred to chemotherapy <14 days after surgery received intervention	<i>Antioxidant:</i> dl- α -tocopherol acetate (1,600 IU qd po beginning 7 days prior to initiation of chemotherapy until development of grade 3 alopecia) <i>Treatment:</i> Fluorouracil, doxorubicin, and cyclophosphamide (FAC)	No difference in alopecia induced by FAC chemotherapy in tocopherol group (100%) and control group (92%) ($P = 0.48$)
1986 Perez [29]	Single-arm trial ($n = 17$, of 20 participants with tumors from multiple sites)	Seventeen women with breast cancer	<i>Antioxidant:</i> α -tocopherol (400 IU qid po beginning 7 days prior to initiation of chemotherapy until development of alopecia) <i>Treatment:</i> Doxorubicin combined with other chemotherapeutic agents	All patients had grade 2 or 3 alopecia after the 3rd course of doxorubicin treatment
<i>Cardiotoxicity</i>				
1980 Weitzman [30]	Randomized, controlled trial ($n = 6$, of 16 participants with tumors from multiple sites)	Six women with breast cancer scheduled to receive doxorubicin Two/six received intervention	<i>Antioxidant:</i> dl- α -tocopherol acetate (1,800 IU qd, route not specified, starting at least 24 h prior to doxorubicin therapy and continuing daily until at least one week after chemotherapy was discontinued) <i>Treatment:</i> Doxorubicin	Systolic time interval (STI) increased for 3/4 control patients and for 2/2 tocopherol treated patients (no statistical tests conducted on breast cancer sub-group)
1982 Legha [31]	Single-arm trial ($n = 21$)	Twenty-one women with metastatic breast cancer (no prior doxorubicin treatment)	<i>Antioxidant:</i> α -tocopherol (2 g/m ² qd po, starting 7 days prior to doxorubicin therapy, and continued as long as patients received doxorubicin, which was as long as the tumor responded to chemotherapy) <i>Treatment:</i> 5-Fluorouracil, doxorubicin, and cyclophosphamide (FAC)	Fifteen percent of patients developed congestive heart failure and >50% of patients developed significant pathological changes in cardiac biopsy tissue. The authors concluded that α -tocopherol does not offer substantial protection against doxorubicin-induced cardiac toxicity

Table 2 continued

Antioxidant supplement Conventional breast cancer treatment Primary outcomes Year author (reference)	Study design (n)	Patient characteristics	Antioxidant intervention & concurrent treatment	Main findings
1983 Lenzhofer [32]	Non-randomized, controlled trial (n = 12)	Twelve women with advanced breast cancer with previous doxorubicin treatment (no prior radiation therapy) Six/twelve received intervention	<i>Antioxidant:</i> Tocopherol (200 mg IM 6 h before doxorubicin infusion) and nifedipine (a calcium channel blocker, 60 mg qd po starting 2 days before infusion and ending 3 days after) <i>Treatment:</i> Doxorubicin	Systolic time intervals (STI) measured over 72 h did not change in pretreated group, compared to untreated group ($P < 0.001$)
Tamoxifen <i>Hot flashes</i> 1998 Barton [33]	Randomized, cross-over, placebo-controlled trial (n = 120)	One hundred and twenty women with a history of breast cancer, with history of at least 14 hot flashes/week × at least 1 month	<i>Antioxidant:</i> Vitamin E succinate (400 IU bid po × 4 weeks) <i>Treatment:</i> 60% on tamoxifen	Crossover analysis showed reduction of one hot flash per day in vitamin E arm compared to placebo arm ($P \leq 0.05$)
Multivitamin Radiation <i>Fatigue</i> 2007 de Souza Fede [39]	Randomized, cross-over, double-blind, placebo- controlled trial (n = 40)	Forty breast cancer patients (no prior radiation therapy)	<i>Antioxidant:</i> Centrum Silver multivitamin (number of tablets per day not specified, taken during half of radiation therapy course) <i>Treatment:</i> Radiation therapy	At the end of first phase, prior to crossover, no improvement in fatigue with multivitamins, compared to placebo (P -value not provided). However, at the end of the second phase, patients on multivitamins reported higher levels of fatigue (25%), when compared to those on placebo (0%, $P = 0.035$)

Table 2 continued

Antioxidant supplement Conventional breast cancer treatment <i>Primary outcomes</i> Year author (reference)	Study design (<i>n</i>)	Patient characteristics	Antioxidant intervention & concurrent treatment	Main findings
Glutamine Chemotherapy <i>Intestinal permeability</i> 2006 Li [40]	Randomized, placebo- controlled trial (<i>n</i> = 60)	Sixty women with breast cancer	<i>Antioxidant:</i> Glutamine (10 g in water tid po, beginning on the first day of neoadjuvant chemotherapy and continuing for at least 12 days) <i>Treatment:</i> Neoadjuvant cyclophosphamide, epirubicin, and fluorouracil (CEF)	<i>Stomatitis:</i> No difference between the two groups ($P > 0.05$) <i>Diarrhea:</i> No difference between the two groups ($P > 0.05$) <i>Intestinal permeability:</i> Increased lactulose/mannitol ratio in the placebo group ($P < 0.05$), indicating worsening of intestinal permeability
<i>Oral mucositis</i> 2006 Peterson [41]	Randomized, placebo- controlled cross-over trial (<i>n</i> = 326)	Three hundred and twenty- six women with breast cancer suitable for treatment with anthracycline-based chemotherapy, who experience moderate to severe oral mucositis during screening cycle of chemotherapy, and who were scheduled to receive at least two additional cycles of treatment	<i>Antioxidant:</i> Glutamine (2.5 g per 5 ml tid po of Saforis, an oral swish and swallow suspension, beginning on the first day of chemotherapy and ending 14 days after treatment) <i>Treatment:</i> FAC; cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF); or doxorubicin and cyclophosphamide (AC)	<i>Oral mucositis incidence:</i> Compared with placebo, Saforis reduced the incidence of clinically significant oral mucositis ($P = 0.026$) <i>Oral mucositis severity:</i> Compared with placebo, Saforis reduced the worst Oral Mucositis Assessment Scale ulceration score ($P = 0.005$)
Glutathione Chemotherapy <i>Urotoxicity</i> 1989 Nobile [42]	Single-arm trial (<i>n</i> = 2, of 13 participants with tumors from multiple sites)	Two women with advanced breast cancer who had not responded to standard chemotherapy	<i>Antioxidant:</i> Glutathione (2.5 g in 100 ml normal saline IV 15 min before and after treatment, repeated q 4 weeks) <i>Treatment:</i> Cyclophosphamide	No observed urotoxicity

Table 2 continued

Antioxidant supplement Conventional breast cancer treatment	Study design (n)	Patient characteristics	Antioxidant intervention & concurrent treatment	Main findings
<i>Primary outcomes</i> Year author (reference)				
Soy isoflavones				
Tamoxifen				
<i>Hot flashes</i> 2000 Quella [46]	Randomized, cross-over, double-blind, placebo- controlled trial (n = 177)	One hundred and seventy- seven women with a history of breast cancer reporting at least 14 hot flashes per week	<i>Antioxidant:</i> Soy isoflavones (50 mg tablets tid po × 4 weeks) <i>Treatment:</i> Could be on tamoxifen or raloxifene if therapy was initiated 4 weeks prior to enrollment	No change in frequency of hot flashes for either group
2002 Van Patten [47]	Randomized, placebo- controlled (n = 123)	One hundred and twenty- three postmenopausal women previously treated for early-stage breast cancer who reported moderate hot flashes	<i>Antioxidant:</i> Soy beverage (90 mg isoflavones qd po × 12 weeks) <i>Treatment:</i> 31% on tamoxifen (stratified by use)	No significant differences between the soy and placebo groups in the number of hot flashes or hot flash scores
2005 MacGregor [48]	Randomized, double-blind, placebo-controlled (n = 72)	Seventy-two women with a history of breast cancer	<i>Antioxidant:</i> Soy isoflavones (17.5 mg capsules bid po × 12 weeks) <i>Treatment:</i> 78% on tamoxifen (stratified by use)	No differences in menopausal symptom scores or quality of life between the two study arms
<i>Tumor response, recurrence, & survival</i> Vitamin C				
Radiation therapy				
<i>Recurrence and survival</i> 1984 Poulter [27]	Non-randomized, controlled trial (n = 52)	Fifty-two women with newly diagnosed breast cancer who had surgical resection of tumor Twenty-seven/fifty-two received intervention	<i>Antioxidant:</i> Ascorbic acid (3 g qd as Redoxon (Roche Ltd.) × 9 months or 5 years (duration unclear)) <i>Treatment:</i> Radiation therapy during 1st 6 weeks of intervention	<i>Five-year disease-free survival:</i> No difference, 48% in ascorbic group and 50% in control group <i>Five-year survival:</i> 55% alive in ascorbic acid group and 71% alive in control group <i>Any recurrence:</i> 7% recurred in ascorbic acid group and 21% recurred in control group

Table 2 continued

Antioxidant supplement Conventional breast cancer treatment <i>Primary outcomes</i> Year author (reference)	Study design (<i>n</i>)	Patient characteristics	Antioxidant intervention & concurrent treatment	Main findings
Antioxidant combination Chemotherapy, radiation, tamoxifen <i>Recurrence and survival</i> 2002 Lesperance [37]	Retrospective observational cohort with matched controls (<i>n</i> = 270)	Women with unilateral non-metastatic breast cancer diagnosed 1989– 1998 who received standard therapy, with (<i>n</i> = 90) and without (<i>n</i> = 180) meta-doses of vitamins and minerals Controls were matched on age at diagnosis, presence of axillary lymph node metastases, tumor stage, grade, estrogen receptor status, year of diagnosis, prescription of systemic therapy	<i>Antioxidant:</i> Varying doses (frequency and duration not specified) of beta-carotene (0–250,000 IU), niacin B3 (0 to >1 mg), vitamin C (0–24 g, selenium (0–1,000 mcg, coenzyme Q10 (dose not specified), and zinc (0 to >50 mg) <i>Treatment:</i> Standard treatment	<i>Recurrence and survival:</i> Breast cancer-specific survival (HR 1.75, 95% CI 0.83–2.69) and disease-free survival (HR 1.55, 95% CI 0.94–2.54) were not improved for the vitamin/ mineral treated group, compared to controls
<i>Survival</i> 1990 Hoffer [34]	Observational cohort study (<i>n</i> = 32, of 132 participants with tumors from multiple sites)	Women with breast cancer who did (<i>n</i> = 27) and did not (<i>n</i> = 5) follow the Hoffer protocol	<i>Antioxidant:</i> Vitamin C (3–40 g qd po; most receive 12 g), vitamin B3 (1.5–3 g qd), vitamin B6 (250 mg qd), folic acid (5– 10 mg qd), other B vitamins (25 or 50 times the RDAs qd), vitamin E (800 LU (sic) qd), beta-carotene (25,000–50,000 LU (sic) qd), selenium (0.2–0.5 mg qd), zinc sulfate (220 mg qd), calcium (sometimes qd), magnesium (sometimes qd), mineral tablet (sometimes qd) (except for vitamin C, route not specified) [35] <i>Treatment:</i> Standard treatment	<i>Survival (months from registration with Hoffer until death or study termination):</i> Length of survival for those receiving Hoffer protocol ranged from 6 to 85 months Length of survival for those who did not follow the Hoffer protocol ranged from 1.8 to 6 months

Table 2 continued

Antioxidant supplement Conventional breast cancer treatment <i>Primary outcomes</i> Year author (reference)	Study design (n)	Patient characteristics	Antioxidant intervention & concurrent treatment	Main findings
1993 Hoffer [35]	Observational cohort study (n = 40, of 170 participants with tumors from multiple sites)	Women with breast cancer who did (n = 37) and did not (n = 4) follow the Hoffer protocol	See Hoffer [34]	<i>Survival (days from registration with Hoffer until death or study termination):</i> Length of survival for those receiving Hoffer protocol ranged from 3 to 1,632 days Length of survival for those who did not follow the protocol ranged from 142 to 1,444 days <i>Two-year survival:</i> No reported deaths (four expected at 18 months, unclear how this was calculated) <i>Tumor response:</i> Partial response in 6/32 patients, no evidence of progression
1994 Lockwood [36]	Single-arm trial (n = 32)	Thirty-two women with “high risk” breast cancer	<i>Antioxidant:</i> Vitamin C (2,850 mg qd po), vitamin E (2,500 IU qd po), beta-carotene (32.5 IU qd po), selenium (387 ug qd po), vitamin A (2,500 IU qd po), vitamin B1 (15 mg qd po), vitamin B2 (15 mg qd po), vitamin B6 (75 mg qd po), vitamin B12 (13 mcg qd po), niacin (45 mg qd po), pantothenic acid (22 mg qd po), folic acid (300 mcg qd po), biotin (300 mcg qd po), vitamin D (300 IU qd po), magnesium (150 mg qd po), zinc (22 mg qd po), copper (3 mg qd po), manganese (6 mg qd po), gamma linolenic acid (1.2 g qd po), omega- 3 fatty acids (3.5 g qd po), and coenzyme Q10 (90 mg qd po) × 24 months <i>Treatment:</i> Varying regimens including surgery, chemotherapy, radiation and tamoxifen	
Tamoxifen <i>Tumor markers</i> 2007 Premkumar [38]	Non-randomized trial (n = 84)	Eighty-four postmenopausal women with resectable breast cancer	<i>Antioxidant:</i> Coenzyme Q10 (100 mg qd po), riboflavin (10 mg qd po), niacin (50 mg qd po) × 90 days <i>Treatment:</i> Tamoxifen	After 45 and 90 days of supplementation, breast cancer patients had a decrease in CEA and CA 15-3 levels, compared to baseline measures (all <i>P</i> < 0.05)

Table 2 continued

Antioxidant supplement Conventional breast cancer treatment	Study design (<i>n</i>)	Patient characteristics	Antioxidant intervention & concurrent treatment	Main findings
<i>Primary outcomes</i> Year author (reference)				
Melatonin				
Chemotherapy				
<i>Tumor response</i> 1999 Lissoni [43]	Single-arm trial (<i>n</i> = 14)	Fourteen women with metastatic breast cancer treated by weekly epirubicin	<i>Antioxidant:</i> Melatonin (20 mg qd po in the evening, starting 7 days prior to chemotherapy and lasting for at least four cycles) <i>Treatment:</i> Epirubicin	<i>Clinical response:</i> Partial response in 5/12 (41%) patients (median duration: 8 months, range 3– 15 months) <i>Thrombocytopenia:</i> Normalization of platelet function in 9/12 (75%) patients
<i>Tumor response and survival</i> 1999 Lissoni [44]	Randomized, controlled trial (<i>n</i> = 77, of 250 participants with tumors from multiple sites)	Seventy-seven women with advanced breast cancer with poor clinical status	<i>Antioxidant:</i> Melatonin (20 mg qd po given in the evening, starting 7 days prior to chemotherapy, continued after chemotherapy interruption, until disease progression) <i>Treatment:</i> Doxorubicin alone, mitoxantrone alone, or paclitaxel alone	<i>Clinical response:</i> Patients on doxorubicin + melatonin had a better partial and complete clinical response when compared to doxorubicin alone (48% vs. 32%, <i>P</i> < 0.05); no differences for mitoxantrone or paclitaxel + melatonin <i>One-year survival:</i> Better for doxorubicin and paclitaxel + melatonin compared to chemotherapy alone (<i>P</i> < 0.05); no difference for mitoxantrone + melatonin
Tamoxifen				
<i>Tumor response</i> 1995 Lissoni [45]	Phase II single-arm trial (<i>n</i> = 14)	Fourteen women with metastatic breast cancer who did not respond to tamoxifen alone (<i>n</i> = 3) or who progressed after initial stable disease (<i>n</i> = 11)	<i>Antioxidant:</i> Melatonin (20 mg po qd in the evening, starting 7 days before tamoxifen and continued until progression) <i>Treatment:</i> Tamoxifen	Partial response in 4/14 (29%) patients (median duration: 8 months, range 3–9 months)

q = every, qd = per day, bid = two times per day, tid = three times per day, qid = four times per day, po = by mouth, IM = intramuscular, IV = intravenous

Effects of antioxidant supplements on tumor response, recurrence, and survival

Nine studies examined the effects of antioxidant supplements on tumor markers ($n = 1$), tumor response ($n = 2$), and recurrence/survival ($n = 6$). The antioxidant supplements in these studies included vitamin C ($n = 1$), combination antioxidants ($n = 5$), and melatonin ($n = 3$).

Vitamin C

We identified only a single study of vitamin C, a non-randomized controlled trial that examined 5-year survival in women who began 3 g per day of ascorbic acid after surgical resection of primary breast cancer and before 6 weeks of radiation therapy ($n = 27$) [27]. Women who had similar clinical histories and did not supplement with ascorbic acid were used as the comparison group ($n = 25$). The duration of treatment with ascorbic acid was not clearly indicated by the report (in different places in the article, overall treatment duration was noted as 9 months and as 5 years). Blood and urine biomarkers collected at regular intervals up to 9 months suggested that women were adherent to vitamin C. The 5-year disease-free survival rates were 48% in ascorbic acid group versus 50% in control group (no statistical tests were reported). The study had significant limitations. The sample size was small; the allocation methods were not described; no information was provided on chemotherapy or hormonal therapy; no adherence information was reported; and no statistical tests were performed to compare the 5-year survival rates.

Combination antioxidants

Five studies examined the effects of antioxidant combinations on recurrence and survival. Lockwood et al. published a single-arm trial ($n = 32$) on the use of high-dose combination antioxidants and other supplements during routine surgery, chemotherapy, radiation therapy, and tamoxifen therapy for breast cancer treatment [36]. The authors reported partial tumor response in 19% of patients, no signs of recurrence in any patients, and no deaths at 24 months. They did not use a concurrently followed control group or compare the observed outcomes to those that would be expected if patients used only conventional treatment. Based on an incompletely described statistical rationale, the authors reported that they had expected four deaths.

Three studies of megadose vitamins were reported from the practice of Abram Hoffer, MD, an orthomolecular physician. Two papers compared observed survival times of cancer patients who did and did not follow a suggested

clinical protocol of mega-dose vitamins [34, 35]. The authors concluded that their data showed better survival for the patients who followed the vitamin protocol than for the control group of patients who did not. However, the appropriateness of this conclusion is unclear given the small control group (five breast cancer patients) and statistical methods. A subsequent well designed study by Lesperance et al. used a retrospective cohort study design with matched controls to examine the effects of Dr. Hoffer's clinical protocol of megadose vitamins on recurrence and survival in women with unilateral non-metastatic breast cancer [37]. Ninety of Dr. Hoffer's patients were matched to 180 control women with breast cancer using multiple clinical criteria; all 270 women received conventional cancer care at the same facility. The study results suggested that the group following Dr. Hoffer's protocol fared worse than the control group, but the differences were not statistically significant (breast cancer-specific mortality hazard ratio: 1.75, 95% CI 0.83–2.69; disease-free mortality hazard ratio: 1.55, 95% CI 0.94–2.54). However, the group treated with megadose vitamins was self-selected and may have had a worse prognosis at study entry.

One study examined the effects of combination antioxidants on tumor markers. Premkumar reported the effects of an antioxidant combination (100 mg coenzyme Q10, 10 mg riboflavin, and 50 mg niacin) on tumor markers in breast cancer patients taking tamoxifen therapy ($n = 84$) [38]. After 3 months, CEA and CA 15-3 ($P < 0.05$) were lower than at baseline.

Melatonin

A series of three trials by Lissoni et al. examined the use of 20 g per day of melatonin on thrombocytopenia, tumor response, and survival during chemotherapy [43, 44], and on tumor response during tamoxifen therapy [45]. A randomized controlled trial ($n = 77$) of melatonin supplementation during chemotherapy found that patients on doxorubicin treatment who took melatonin had a better clinical response than those on doxorubicin alone (48% vs. 32%, $P < 0.05$) (no differences for those on mitoxantrone or paclitaxel) [44]. Patients taking melatonin with doxorubicin or paclitaxel had better survival than those taking doxorubicin or paclitaxel alone ($P < 0.05$) (no difference for mitoxantrone). This group also reported two other single-arm trials. A single-arm trial ($n = 14$) of melatonin supplementation during epirubicin treatment showed normalization of platelet function in 9/12 patients (75%) and tumor response in 41% of patients [43]. A phase II single-arm trial ($n = 14$) in metastatic breast cancer patients taking tamoxifen showed a partial response in 4/14 patients [45].

Discussion

Data on the effects of antioxidant supplements during conventional breast cancer treatment are scarce. Overall, the 22 articles we identified provided insufficient evidence to support conclusions regarding the effects of individual antioxidant supplementation during conventional breast treatment on toxicities, tumor response, recurrence, or survival. However, for several antioxidant supplements, studies suggested possible beneficial, null, or harmful effects and require further investigation. A few studies indicated that specific supplements may decrease side effects associated with treatment, including vitamin E for hot flashes due to hormonal therapy and glutamine for oral mucositis during various chemotherapy regimens. Underpowered trials suggested that melatonin supplementation may enhance tumor response during epirubicin and doxorubicin treatment, and prolong survival after doxorubicin treatment. Trials indicated that vitamin E was not useful in preventing alopecia or cardiotoxicity due to chemotherapy. One study showed that taking multivitamins during radiation treatment increased fatigue. An observational study suggested that megadose supplements did not improve, and may have decreased, 5-year survival rates.

All of the studies suffered from methodological limitations. None of the studies adequately measured both the short- and long-term effects of antioxidant supplementation during breast cancer treatment. Many studies had other limitations including not having a well matched control population, using small sample sizes that lacked sufficient power to make definitive conclusions, including populations heterogeneous in their conventional treatments, and/or not following patients long enough to make conclusions on recurrence and survival rates. Another limitation of the studies presented here is that none accounted for other behaviors or exposures that may alter the effects of antioxidant supplements, such as intake of other dietary supplements, dietary antioxidant intake via fruits and vegetables, host nutritional status, and physical activity patterns.

Caution is nonetheless warranted on the use of antioxidant use during breast cancer treatment. The only large-scale observational study of breast cancer patients using high-dose antioxidants during treatment showed a trend towards decreased survival [37]. No large-scale clinical trials of antioxidants during any form of breast cancer treatment have been conducted with recurrence or survival as the outcome. A recent review of the evidence regarding early and late effects of the use of antioxidants during chemotherapy and radiation therapy for multiple tumor sites concluded that antioxidant supplementation may cause harm during radiation therapy, but may possibly reduce dose-limiting toxicities during chemotherapy [49].

Because breast cancer patients may receive different forms and doses of chemotherapy and radiation therapy than patients with other cancers, these conclusions may not be specifically applicable to breast cancer patients even if they are valid for patients with other cancers. Unfortunately, few of the studies presented long-term survival data. To date, the strongest evidence suggesting the possibility of harm comes from a study of antioxidant supplements during radiation therapy for head and neck cancers. A well designed and well powered randomized, clinical trial examined the use of α -tocopherol supplementation (400 IU/day for 3 years, beginning at the initiation of radiation therapy) during radiation therapy on treatment related side effects and overall survival [50, 51]. The investigators found that the treated patients had both fewer adverse side effects and poorer overall survival than the controls at 8 years. However, head and neck cancer patients differ from breast cancer patients in risk factors, treatment, and prognosis. Hence these study results may or may not be generalizable to breast cancer patients. Finally, no studies have examined the effects of antioxidant supplementation during hormonal therapy on breast cancer survival.

Observational studies now in progress will be better able to address questions on the effects of using antioxidant supplements during breast cancer treatment. A review of NIH-funded studies (<http://crisp.cit.nih.gov/>) identified two well designed, prospective observational studies currently collecting data on these outcomes and CAM use and lifestyle factors; their results will significantly contribute to the knowledge base in this area. One study (SWOG S0221A-ICSC, PI: Ambrosone) is examining the effects of supplemental antioxidants on treatment outcomes among patients ($n = 3,250$) in a therapeutic trial of adjuvant doxorubicin, cyclophosphamide and paclitaxel for breast cancer. Another, the Pathways Study (R01CA105274, PI: Kushi), is using rapid case ascertainment to identify women within Kaiser Permanente Northern California who are diagnosed with invasive breast cancer ($n = 3,000$) [52]. The study will follow women over time to investigate effects of lifestyle and molecular factors, including diet, supplement use, and genetic polymorphisms, in addition to treatment, on long-term outcomes. Women with breast cancer are not using antioxidant supplements in isolation; women who use antioxidants are more likely to use other dietary supplements, other forms of complementary and alternative medicine, and modify their diets and physical activity [53, 54]. Observational studies can collect data on multiple exposures in real-life contexts. If powered sufficiently, these studies can provide us with information on the combined effects of multiple simultaneous exposures.

Well designed clinical trials offer the best opportunities to draw definitive conclusions on single agents or agent

combinations because they can control for dose, duration of use, and timing of use. A review of NIH's clinical trials database (<http://www.clinicaltrials.gov>) yielded four trials examining the effects of antioxidant supplements specifically during breast cancer treatment on treatment-related toxicities (four trials during chemotherapy, and one trial during tamoxifen therapy). Two trials are examining the effects of antioxidant supplements on chemotherapy-related treatment toxicities; CoQ10 for fatigue during chemotherapy and radiation therapy (phase of trial unspecified, PI: Lesser) and a phase III trial of glutamine for peripheral neuropathy during paclitaxel chemotherapy (PI: Vahdat). A phase II trial is examining the effects of glutathione during doxorubicin and cyclophosphamide treatment on tumor response (PI: Montereau), and another phase II trial is examining the use of soy isoflavones during tamoxifen therapy to alleviate hot flashes (Chair: Fleming).

Currently, the evidence is insufficient to provide clear guidelines on the use of antioxidant supplement during breast cancer treatment, including radiation therapy, chemotherapy, and hormonal therapy. It is important for patients and clinicians to know if antioxidant interventions during conventional breast cancer treatment can decrease dose-limiting toxicities and long-term side effects. If so, supplementation could enable patients to receive higher doses and to be more adherent to treatment. It is also important to know if antioxidant supplementation is beneficial or detrimental to breast cancer recurrence and survival. This review suggests that well designed clinical trials and observational studies are needed to provide this information.

Priority in trial development should be given to agents that show the most promise of either reducing treatment toxicities (e.g., glutamine to reduce oral mucositis) or enhancing treatment effects (e.g., melatonin to enhance tumor response). Trials should follow the standard three-phase sequence and evaluate magnitude of effect, short-term adverse effects, and interactions with conventional treatments. Phase III trials should follow enough study participants long enough to assess effects on recurrence and survival.

The purpose of conducting trials is to determine whether an intervention that is thought to be beneficial really is beneficial. The medical community has repeatedly made mistakes by adopting treatments prior to rigorous evaluation. Trials of antioxidant supplements are needed because many people believe that such supplements are beneficial and are using them in the absence of evidence for benefit or harm. Given the prevalence of such use, the absence of clear evidence for harm justifies trials, but we and others must strive to maintain clinical equipoise and rigor in conducting them.

Meanwhile, in the absence of clear evidence, clinicians should discuss the potential risks and benefits of using

antioxidant supplements during treatment with their breast cancer patients.

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