

A randomized, double-blind, placebo-controlled study of oral coenzyme Q₁₀ to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer

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Background Coenzyme Q₁₀ (CoQ₁₀) is a common antioxidant supplement with known cardioprotective effects and potential anticancer benefits.

Objectives We performed a randomized, double-blind, placebo-controlled study of oral CoQ₁₀ in female breast cancer patients with the primary objective of determining CoQ₁₀'s effects on self-reported fatigue, depression, and quality of life (QOL).

Methods Eligible women with newly diagnosed breast cancer and planned adjuvant chemotherapy were randomized to oral supplements of 300 mg CoQ₁₀ or placebo, each combined with 300 IU vitamin E, divided into 3 daily doses. Treatment was continued for 24 weeks. Blood tests, QOL measures, and levels of plasma CoQ₁₀ and vitamin E were obtained at baseline and at 8, 16, and 24 weeks. Mixed-effects models were used to assess treatment differences in outcomes over time.

Results Between September 2004 and March 2009, 236 women were enrolled. Treatment arms were well balanced with respect to age (range, 28–85 years), pathologic stage (stage 0, 91%; stage I, 8%; stage II, 1%), ethnicity (white, 87%; black, 11%; Hispanic, 2%), and planned therapy. Baseline CoQ₁₀ levels in the CoQ₁₀ and placebo arms were 0.70 and 0.73 μg/mL, respectively; the 24-week CoQ₁₀ levels were 1.83 and 0.79 μg/mL, respectively. There were no significant differences between the CoQ₁₀ and placebo arms at 24 weeks for scores on the Profile of Mood States–Fatigue questionnaire (least squares means, 7.08 vs 8.24, $P = .257$), the Functional Assessment of Chronic Illness Therapy–Fatigue tool (37.6 vs 37.6, $P = .965$), the Functional Assessment of Cancer Therapy–Breast Cancer instrument (111.9 vs 110.4, $P = .577$), or the Center for Epidemiologic Studies–Depression scale (11.6 vs 12.3, $P = .632$).

Conclusions Supplementation with conventional doses of CoQ₁₀ led to sustained increases in plasma CoQ₁₀ levels but did not result in improved self-reported fatigue or QOL after 24 weeks of treatment.

Published data suggest that at least 80% of cancer patients who are undergoing treatment, especially multimodality therapy, experience a significant degree of fatigue that may

negatively impact their quality of life (QOL), emotional well-being, and treatment tolerance.^{1–11} Compared with fatigue experienced by those without cancer, cancer-related fatigue is typically more severe and not reliably relieved by

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rest.¹² Up to 80% of women receiving adjuvant breast cancer therapy may experience significant cancer- and treatment-related fatigue.¹³ Persistent fatigue may affect a significant number of these women; published data suggest that it may last for months or years after the completion of therapy in at least 30% of patients with solid tumors or hematologic malignancies.^{14–18} For example, 81% of 1,372 women with breast cancer who had completed primary treatment described fatigue during or following their therapy.¹⁹

Patients perceive fatigue to be the most distressing symptom associated with their cancer experience, even worse than pain or nausea and vomiting.⁴ However, studies suggest that fatigue usually does not exist in isolation but rather as part of a symptom cluster that often includes depression, difficulty sleeping, and pain.^{13,20} Current clinical practice guidelines recommend a regular assessment of fatigue in all cancer patients during and following their treatment,^{21,22} and several validated self-assessment tools for fatigue are available.²³

Multiple recent reviews summarizing pharmacologic and nonpharmacologic approaches to treating cancer-related fatigue have been published;^{24–27} unfortunately, relatively few pharmacologic interventions have been efficacious. Coenzyme Q₁₀ (CoQ₁₀, also known as ubiquinone) is a fat-soluble quinone with properties similar to those of vitamins.²⁸ It is an antioxidant and a redox coenzyme of the respiratory chain^{29–31} that occurs naturally in the organs of most animal species,³² as well as in relatively high levels in the heart, liver, kidney, and pancreas of humans.²⁸ Biochemically, CoQ₁₀ works by (1) having a direct regulatory role on succinyl and the reduced form of nicotinamide adenine dinucleotide dehydrogenases, (2) acting as a catalyst and playing an integral role in regulating the cytochrome *bc1* complex, and (3) possibly having direct membrane-stabilizing properties that are separate from its role in oxidative phosphorylation.^{28–33} Thus, CoQ₁₀ works within human cells to create energy for cell growth and maintenance.^{30,34,35}

Oral CoQ₁₀ is well absorbed, although rather slowly, with peak plasma levels occurring 5 to 10 hours after ingestion.³⁶ Normal plasma levels of CoQ₁₀ range between 0.64 and 1.06 $\mu\text{g}/\text{mL}$ plasma.^{37–45} Males have higher levels than do females; older adults have lower levels of CoQ₁₀ than do younger adults.⁴⁶ The typical US diet provides approximately 5 to 10 mg of CoQ₁₀ per day. Side effects of CoQ₁₀ may include insomnia, elevated liver enzymes, rash, nausea, epigastric pain, dizziness, photophobia, irritability, headache, and heartburn,^{47,48} however, regardless of the dosage used, few untoward effects have been observed.⁴⁹

Although CoQ₁₀ has been used for several decades as a dietary supplement for general health maintenance, the benefits of its administration have been most extensively evaluated in a variety of cardiovascular and neurodegenerative conditions. In patients with congestive heart failure, CoQ₁₀ supplementation to standard medical therapy improved QOL, New York Heart Association classification, and congestive symptoms including shortness of breath and edema.^{47,50–53} Similar benefits were seen in a study of patients with hypertrophic cardiomyopathy.⁵⁴ Ongoing CoQ₁₀ administration has led to sustained decreases in both systolic and diastolic blood pressure.⁵⁵ Finally, data suggest that high-dose CoQ₁₀ administration may slow the functional decline experienced by patients with early-stage Parkinson's disease.⁴¹

In light of its role in mitochondrial energy generation, CoQ₁₀ supplementation has been evaluated in a variety of patient populations with fatigue. It has been clearly demonstrated to improve the symptoms of weakness and fatigue in the rare patient with inherited defects in CoQ₁₀ biosynthesis.^{56,57} Administration of CoQ₁₀ also has beneficial effects on dyspnea and exercise tolerance—cardiac fatigue—in patients with congestive heart failure and/or cardiomyopathy.^{29,39,47} However, conflicting data exist regarding the effect of CoQ₁₀ on fatigue in a normal population. Cooke et al⁵⁸ described a trend toward an increased time to exhaustion following 2 weeks of CoQ₁₀ intake. A number of other placebo-controlled studies failed to demonstrate an improvement in physical functioning in similar trained and untrained populations.^{59–63}

Clinical and epidemiologic investigations of CoQ₁₀ in cancer are limited, and the few small studies that have been reported have evaluated the ability of CoQ₁₀ supplementation to ameliorate or prevent cardiotoxicity in patients receiving anthracycline chemotherapy.^{64,65} Coenzyme Q₁₀ is a common supplement used by patients with breast and other cancers; its purported benefits include improved cancer- and treatment-related fatigue.⁶⁶ However, no prospective data have been published on the efficacy of this supplement in the fatigued cancer population. As a result, we performed a randomized, double-blind, placebo-controlled study of CoQ₁₀ in women with breast cancer who were beginning adjuvant chemotherapy. The primary aim of this trial was to assess the effect of CoQ₁₀ supplementation on treatment-induced fatigue in these women; a secondary goal was to assess the compound's effects on overall QOL and depression.

Methods

Patient population

Women with newly diagnosed breast cancer who were scheduled to receive adjuvant chemotherapy were eligible

for this randomized, placebo-controlled, double-blind trial. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , ability to provide written informed consent, a hemoglobin level ≥ 11 g/dL, a total cholesterol level ≥ 160 mg/dL, a bilirubin level $\leq 1.5 \times$ upper limit of normal (ULN), a plasma glutamic oxaloacetic transaminase level $\leq 2.5 \times$ ULN, and a plasma glutamate pyruvate transaminase level $\leq 2.5 \times$ ULN. Additional ineligibility criteria included an involuntary loss of $>5\%$ of body weight in the previous 3 months; current or planned statin therapy; current or planned use of medications for fatigue, including corticosteroids (other than an allowable intermittent use as part of a chemotherapy regimen), amphetamines, or other stimulants including methylphenidate or modafinil; uncontrolled hypertension; pregnancy; uncontrolled thyroid dysfunction; and current or planned anticoagulant therapy (except for maintenance of catheter patency). The study was approved by the Institutional Review Board of the Wake Forest School of Medicine and by each participating site's review board. All study participants provided written informed consent.

Treatment

Eligible patients were stratified by type of chemotherapy (anthracycline vs no anthracycline) and whether or not they received radiation as part of their treatment course. Participants were then randomized to receive daily oral supplements of either 300 mg CoQ₁₀ (Soft Gel Technologies, Los Angeles, California) per day or placebo—each combined with 300 IU vitamin E (Soft Gel Technologies, Los Angeles, California)—divided into 3 doses daily of either 100 mg CoQ₁₀ or placebo plus 100 IU vitamin E. Vitamin E served as a lipid carrier to improve absorption of the lipophilic CoQ₁₀ molecule. Placebo or CoQ₁₀ supplements were begun no later than 4 days after chemotherapy initiation; they were taken 3 times daily with food for 24 weeks. Participants were instructed to avoid taking any additional supplements containing CoQ₁₀ or vitamin E for the duration of the study. Adherence to study medications was assessed by serial measures of serum CoQ₁₀ and vitamin E levels at baseline and following 8, 16, and 24 weeks of therapy.

Outcome measures

Several QOL instruments were used to provide data on the primary outcome of fatigue as well as secondary end points including overall QOL, depression, and social support, all of which could affect fatigue in a given patient. Fatigue was measured via the POMS-F (a 7-question fatigue subscale of the Profile of Mood States assessment

tool, in which items are rated for the past week on a 5-point scale ranging from 0 [not at all] to 4 [extremely]),⁶⁷⁻⁷⁰ the FACIT-F (a 13-item fatigue scale from the Functional Assessment of Chronic Illness Therapy measurement system, in which items are rated from 0 [not at all] to 4 [very much]),^{71,72} and a self-reported Linear Analog Scale Assessment-Fatigue (LASA-Fatigue), in which patients were asked to rate their overall level of fatigue using a 100-mm line with the anchors of “absolutely no fatigue” at 0 and “the worst possible fatigue imaginable” at 10.

We assessed QOL via the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) instrument, which provided an assessment of the patients' health status in addition to specific breast cancer related concerns.⁷³ Depressive symptomatology was assessed by the short form (8-item) Center for Epidemiologic Studies-Depression scale (CES-D).⁷⁴ The social support of participants was measured, as a control variable, using the 20-item Medical Outcomes Study Social Support Survey.⁷⁵ All symptom and QOL assessments were measured at baseline and again following 8, 16, and 24 weeks of study treatment.

Analytical method for α -tocopherol (vitamin E)

α -Tocopherol was quantified by reverse-phase, high-performance liquid chromatography (HPLC) via a modification of the method reported by Hess et al.⁷⁶ All sample-handling steps were performed under subdued amber lighting. Patient plasma samples were collected from October 2004 to September 2009 and stored at -80°C until they were analyzed. Coenzyme Q₁₀ is stable for several years when it is stored at -80°C .⁷⁷ Prior to extraction, 50 μL of 25 $\mu\text{g}/\text{mL}$ vitamin K (used as an internal standard in place of the tocol used by Hess et al⁷⁶) was added to 200 μL plasma and 1 mL ethanol containing 30 μM butylated hydroxytoluene (BHT). The solution was extracted twice with 2-mL aliquots of hexane. The combined hexane extracts were evaporated to dryness under nitrogen, then reconstituted with 200 μL ethanol containing 30 μM BHT. Duplicate 35- μL aliquots were subjected to reverse-phase HPLC using a Beckman Ultrasphere C18 (4.6 \times 250 mm; Beckman Coulter, Brea, California) analytical column at 25°C . The isocratic mobile phase was composed of acetonitrile/tetrahydrofuran/methanol/1% ammonium acetate (684:220:68:28 by volume) at a flow rate of 1.5 mL/min. The eluted components were detected at 290 nm (vitamin E) and 269 nm (vitamin K) via a variable wavelength detector programmed to monitor the 2 wavelengths during different time segments of separation.

Analytical method for CoQ₁₀

We quantified CoQ₁₀ following complete oxidation to ubiquinone with CuCl₂ using a modification of the method reported by Kaikkonen et al.⁷⁷ Plasma samples (200 μL) were mixed with 1 mL ethanol (containing no BHT) and 50 μL of 25 μg/mL vitamin K. Oxidation was performed by addition of 200 μL of 2 mM CuCl₂ at room temperature and in the dark for 30 minutes. The reaction mixture was then rapidly extracted twice with 4-mL portions of hexane. The combined hexane extracts were evaporated to dryness under nitrogen and then reconstituted with 200 μL of ethanol. Duplicate 35-μL injections were subjected to reverse-phase HPLC under the same conditions used for vitamin E. The column eluent was monitored at 325 nm (vitamin K) and 270 nm (CoQ₁₀).

Statistical considerations

The primary objective of this randomized trial was to assess the effect of CoQ₁₀ on self-reported cancer treatment-related fatigue in breast cancer patients following 24 weeks of therapy. Secondary objectives were to assess the effect of CoQ₁₀ on overall QOL and depression. Patients were stratified by planned radiation therapy (yes/no) and type of chemotherapy (anthracycline vs no anthracycline) and assigned within strata to receive CoQ₁₀ or a placebo with equal probability via variably sized permuted block randomization. The study was powered to detect a 30% relative difference in the POMS-F subscale (ie, 9.9 vs 6.9) between the 2 groups with 90% power at the 5% 2-sided level of significance, with assumptions of an adjusted standard deviation (SD) of 5.9 for the POMS-F subscale, a dropout rate of approximately 40%, and an allowance for 1 interim look. The required sample size was 118 per group.

Chi-squared, Fisher's exact, and Wilcoxon's rank-sum tests were used to assess baseline group differences in categorical and continuous variables. Repeated measures analysis of variance (RM-ANOVA) was used to assess the effect of CoQ₁₀ on each outcome over time. Models were constrained to have equal group means at baseline, as proposed by Fitzmaurice et al.⁷⁸ This approach gives the same estimate of treatment effect as does an RM-ANCOVA model (ie, the baseline measure of the outcome is used as a covariate) when there are no missing data; but our approach uses all the data, even data on participants who are missing at baseline and those who have only baseline observations, which allows us to use more data. Various covariance structures were considered for each model, including unstructured, compound symmetry, autoregressive, and Toeplitz; and the Bayesian information criterion was used to choose the most appropriate

covariance structure for each outcome. Age, race, body mass index (BMI), and strata were included as covariates in separate models. The primary interest was in the effect of CoQ₁₀ at 24 weeks, and this effect was assessed by using a linear contrast within the RM-ANOVA. The same modeling strategy was used to assess the effect of CoQ₁₀ on the secondary outcome measures.

Results

In all, 236 patients were enrolled between August 2004 and March 2009 (Figure 1). Baseline characteristics for all participants are summarized in Table 1. Ages ranged from 28 to 85 years, with a median of 51 years. Most patients were non-Hispanic whites (87%); 2% were Hispanic, and 11% were non-Hispanic blacks. Most patients were receiving anthracycline chemotherapy (84%); 61% also received radiation therapy. In all, 91% of the patients had an ECOG performance status of 0. Levels of CoQ₁₀ ranged from 0.13 to 3.4 μg/mL, with a median of 0.67 μg/mL; 44% of the patients had CoQ₁₀ levels that were lower than normal (<0.64 μg/mL). Patients reported low levels of fatigue at study initiation. Patient characteristics did not differ significantly between the treatment groups.

Plasma CoQ₁₀ and vitamin E levels were measured at baseline and following 8, 16, and 24 weeks of therapy. These data are summarized in Figures 2 and 3 for all samples collected at each visit. On average, CoQ₁₀ supplementation resulted in an approximately 3-fold increase in plasma levels of CoQ₁₀, from a mean (SD) of 0.7 (0.4) μg/mL at baseline to 2.2 (1.2) μg/mL at 8 weeks. However, there was much variability in postrandomization levels, and several patients failed to have noticeable increases in their levels; the average posttreatment CoQ₁₀ levels were lower than the baseline levels for 12% of the participants on the CoQ₁₀ arm. All patients received vitamin E supplementation, and levels almost doubled from 13.8 (8.7) μg/mL at baseline to 24.1 (15.1) μg/mL at 8 weeks. Average posttreatment vitamin E levels were lower than baseline levels for 11% of the participants.

The primary objective of this study was to assess the effect of CoQ₁₀ on patients' self-reported fatigue levels at 24 weeks postrandomization. Fatigue was quantified primarily by the POMS-F subscale. The FACIT-F subscale and LASA-Fatigue were also used to quantify fatigue. Higher values for the FACIT-F subscale and lower values for the POMS-F subscale and the LASA-Fatigue indicate less fatigue. The raw fatigue measures over time are summarized in Table 2, and the least squares means adjusted for covariates are shown in Table 3. As expected, fatigue increased significantly with the onset of chemotherapy ($P < .001$) for patients in both groups and gradually lessened thereafter, although never to pretreatment

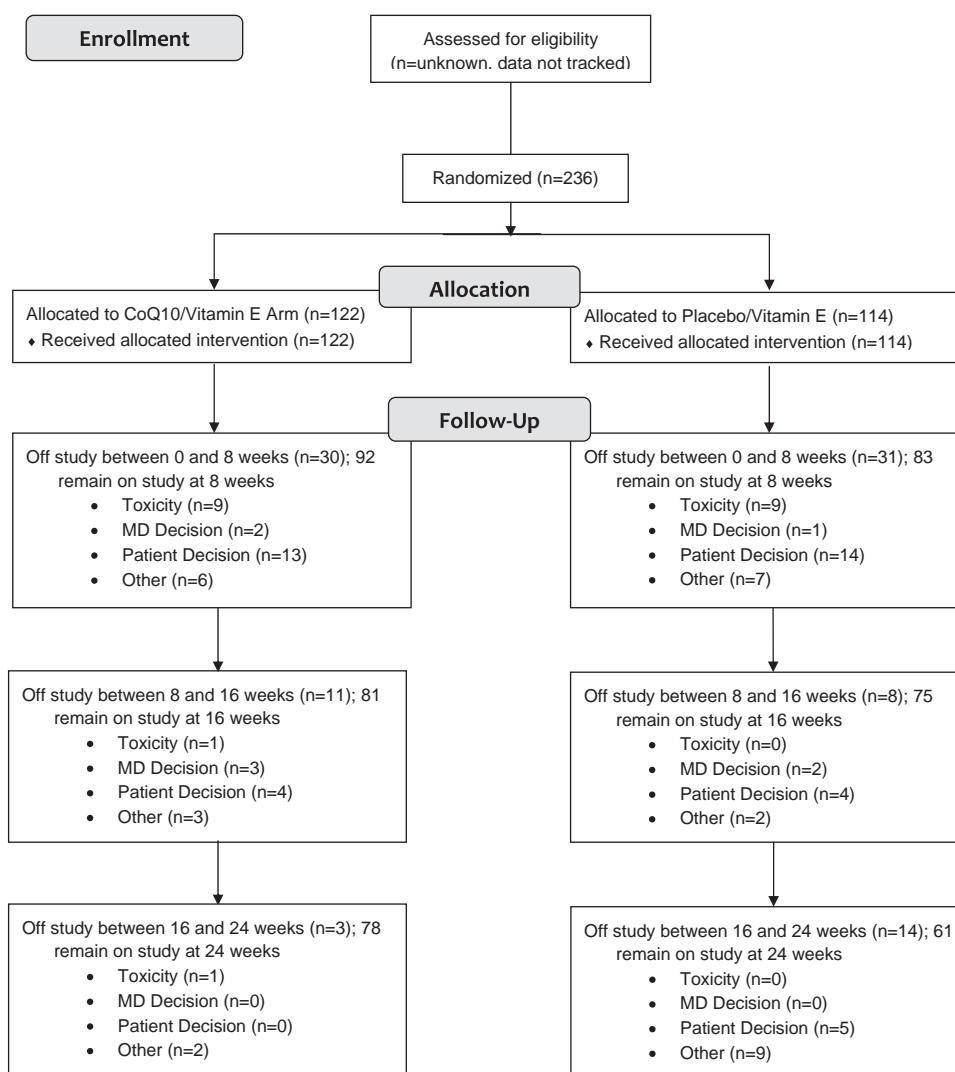


FIGURE 1 Consort flow diagram of patients enrolled in this trial.

levels. In comparison to the placebo arm, CoQ₁₀ supplementation was not significantly associated with changes in any of the fatigue measures at 24 weeks or at any time during this study. The interaction between baseline CoQ₁₀ levels and treatment was not significant, and the interaction between baseline fatigue and treatment was not significant in separate RM-ANCOVA models, indicating that the treatment effect did not differ depending on initial fatigue or CoQ₁₀ levels. Separate models that were examined for the subgroup of patients whose CoQ₁₀ levels were below normal at baseline also failed to show any treatment benefit for CoQ₁₀, as did models that were run on the patients in the lowest quartile of fatigue (worst fatigue) at baseline. We also examined the treatment effect in patients who were somewhat compliant (defined here as having a 20% increase in vitamin E levels from

baseline to posttreatment assessments). Again, there was no significant benefit to CoQ₁₀ in this group of patients.

As expected, patients in both treatment groups experienced decreases in their overall QOL ($P < .001$), as seen in Table 4. Treatment with CoQ₁₀, however, did not significantly improve the patients' QOL at 24 weeks, as measured by the FACT-B total score ($P = .764$ overall, $P = .577$ at 24 weeks). Nonsignificant increases in depressive symptoms after the initiation of adjuvant therapy were noted, and these symptoms were also not significantly different between the CoQ₁₀ and the placebo groups ($P = .697$ overall, $P = .632$ at 24 weeks).

Grade 3 and 4 toxicities that were experienced by patients in this trial are summarized in Table 5. No severe drug-related toxicity was assessed as possibly, probably, or definitely attributed to CoQ₁₀. Placebo and CoQ₁₀ pa-

TABLE 1 Patient characteristics

Characteristic	CoQ ₁₀	Control (Vitamin E)	P
Total no. (%)	122 (100)	114 (100)	
Age			.239
Median, y (range)	52 (31–85)	50 (28–72)	
≥50 y, no. (%)	72 (59)	60 (53)	
BMI			.133
Median (range)	27.3 (18.8–53.2)	29.7 (18.4–50.8)	
Underweight-normal (<25), no. (%)	38 (31)	35 (31)	
Overweight (25–30), no. (%)	46 (38)	25 (22)	
Obese (≥30), no. (%)	37 (31)	54 (47)	
Race/ethnicity			.505
Hispanic, no. (%)	3 (2)	1 (1)	
Black, no. (%)	15 (12)	11 (10)	
White, no. (%)	104 (85)	102 (89)	
ECOG Performance status			.815
0, no. (%)	112 (92)	103 (90)	
1, no. (%)	10 (8)	10 (9)	
2, no. (%)	0 (0)	1 (1)	
Stratum			—
Anthracycline + radiotherapy, no. (%)	61 (50)	59 (52)	
Anthracycline, no radiotherapy, no. (%)	40 (33)	38 (33)	
Nonanthracycline + radiotherapy, no. (%)	14 (11)	11 (10)	
Nonanthracycline, no radiotherapy, no. (%)	7 (6)	6 (5)	
Plasma CoQ ₁₀ level (μg/mL), median (range)	0.63 (0.13–3.40)	0.72 (0.23–1.73)	.152
Plasma vitamin E level (μg/mL), median (range)	11.1 (0.6–52.2)	11.3 (3.1–51.1)	.890
POMS-F score, median (range)	4.0 (0–27)	4.0 (0–28)	.949
FACIT-F score, median (range)	44.0 (10–52)	42.0 (11–52)	.141
LASA-Fatigue score, median (range)	2.0 (0–9)	2.0 (0–8)	.808

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; POMS, Profile of Mood States–Fatigue; FACIT, Functional Assessment of Chronic Illness Therapy–Fatigue; LASA, Linear Analog Scale Assessment.

tients did not differ significantly in the incidence of grade 3 and 4 toxicities ($P = .301$) or any toxicity (all grades) ($P = .430$).

Discussion

The primary aim of this randomized, double-blind, placebo-controlled trial was to determine the effect of CoQ₁₀ supplementation on self-reported fatigue in women who had breast cancer and were beginning adjuvant chemotherapy. Despite a host of clinical trials, relatively few pharmacologic interventions for cancer-related fatigue have been effective. Erythropoiesis-stimulating agents have improved fatigue in a number of prospective, randomized, phase III clinical trials of anemic cancer patients receiving chemotherapy;⁷⁹ however, recent concerns over tumor stimulation and decreased survival fol-

lowing the use of these agents have significantly curtailed their use. A subset of patients who had more severe fatigue and/or advanced disease benefited somewhat from treatment with the psychostimulant methylphenidate in a phase III trial reported by Moraska et al,⁸⁰ although no benefit was seen in the study population as a whole. Similar results were seen in more than 800 patients who were treated in a phase III trial of modafinil, a nonamphetamine psychostimulant, in which only those patients with severe baseline fatigue seemed to benefit.^{81,82}

In this trial, despite serologic evidence of an average 3-fold increase in CoQ₁₀ levels in women on the treatment arm, no difference in fatigue between CoQ₁₀-supplemented and placebo-treated patients was seen according to 3 separate, validated measures. This was true for patients with below-normal CoQ₁₀ levels at baseline

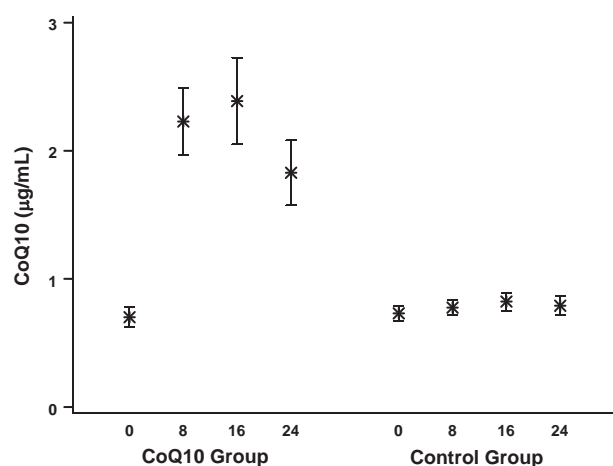


FIGURE 2 Mean plasma CoQ₁₀ levels (with 95% CI) at baseline and 8, 16, and 24 weeks by treatment group.

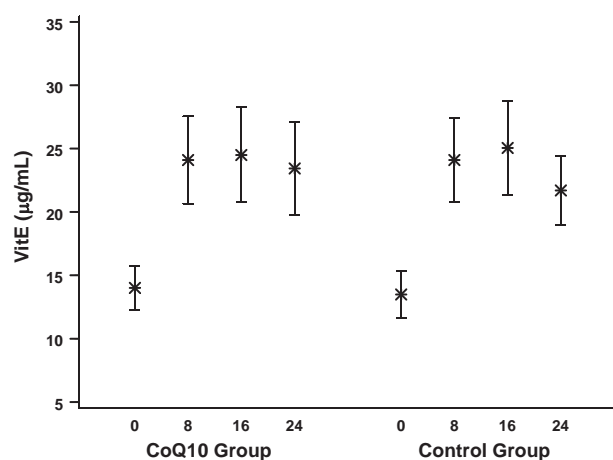


FIGURE 3 Mean vitamin E levels (95% CI) at baseline and 8, 16, and 24 weeks by treatment group.

and for patients with worse fatigue at baseline, subgroups that might be more likely to benefit from CoQ₁₀ supplementation. The fatigue trajectory seen in these patients (ie, fatigue that worsened with treatment and only gradually returned toward baseline after almost 6 months) mirrors the observations seen in previously published trials of fatigue in newly diagnosed women with breast cancer. Although not efficacious, CoQ₁₀ supplementation was devoid of significant toxicity; adverse events seen in these patients represented the side effects of chemotherapy with or without radiation therapy.

One reason for the widespread use of CoQ₁₀ supplementation by patients with breast and other cancers has been to correct a perceived CoQ₁₀ deficiency that is thought to predispose patients to an increase in treatment-related toxicity. Deficiency of CoQ₁₀ has been described in a cohort

of 200 women who were hospitalized for breast surgery for both malignant and nonmalignant lesions.⁸³ In our study, CoQ₁₀ levels at baseline were below the lower limit of normal^{38-40,84} for approximately 44% of enrolled women. Supplementation with standard doses of CoQ₁₀ led to a significant and sustained increase in plasma CoQ₁₀ levels in treated patients in this trial. Although a variety of factors can influence plasma CoQ₁₀ levels (eg, age, race, plasma lipid levels, and use of concurrent medications such as statins), the steady-state plasma CoQ₁₀ levels that were seen in treated women in this trial mirror those described in other patient populations that were supplemented with similar amounts of CoQ₁₀.^{39-41,84}

This trial did not address the benefits, if any, of CoQ₁₀ dose escalation. The safety of escalated doses of CoQ₁₀ has been evaluated in a randomized, placebo-controlled trial in patients with early Parkinson's disease. A total of 80 patients received doses of 300 mg to 1,200 mg per day of CoQ₁₀ for up to 16 months, and there was no difference in the incidence of drug-related toxicities between the placebo and treatment arms.⁴¹ Doses of up to 3,000 mg/day for up to 8 months have also been well tolerated in cohorts of patients with Parkinson disease and amyotrophic lateral sclerosis.^{85,86} Although treated patients in all of these trials experienced a low incidence of gastrointestinal side effects (including nausea, vomiting, diarrhea, and abdominal discomfort), these symptoms did not appear to be dose-related and occurred at identical rates in both treatment and placebo arms.^{41,47,87,88} In this trial, dose escalation of CoQ₁₀ was not attempted. However, no evidence of an improvement in fatigue was seen in patients with the highest sustained levels of CoQ₁₀ following supplementation (100% increase or more). Although this result does not rule out a possible benefit of higher doses, it provides no suggestion of a "dose response" in the population of women enrolled in this trial.

A large number of patients dropped out before the 24-week study end point. However, the causes for study discontinuation were not different between the 2 treatment arms. Of the 97 patients who withdrew before the scheduled final study assessment, 21% did so for toxicities related to their primary anticancer therapy. Another 41% of these patients discontinued therapy following prolonged periods of inability to reliably tolerate oral medications. Again, this was primarily related to treatment-induced toxicities, particularly hospitalization, nausea, and/or vomiting, as well as an unwillingness to comply with a 3 times-a-day dosing regimen of study medications in the face of a perceived daunting schedule of antitumor therapy. In light of this dropout rate, we also analyzed all primary and secondary end points at the interim 8- and 16-week time

TABLE 2 Summary of fatigue measures over time

Outcome	Week	No.	CoQ ₁₀		Control (vitamin E)		
			Mean	SD	No.	Mean	SD
POMS-F (range, 0–28)	0	120	5.59	6.06	113	5.69	6.09
	8	92	9.92	7.05	81	9.32	7.61
	16	79	8.62	7.05	72	8.89	7.87
	24	78	6.65	6.52	61	8.43	7.66
FACIT-F (range, 0–52)	0	120	41.0	9.69	113	38.9	10.6
	8	92	34.1	12.1	81	34.4	11.8
	16	80	35.3	11.6	72	35.9	12.1
	24	76	38.9	11.3	61	36.9	12.0
LASA-Fatigue (range, 0–10)	0	118	2.36	2.14	112	2.54	2.34
	8	90	3.91	2.58	80	4.19	2.67
	16	80	3.93	2.53	73	3.71	2.62
	24	77	2.92	2.36	61	3.52	2.49

Abbreviations: POMS, Profile of Mood States–Fatigue; FACIT, Functional Assessment of Chronic Illness Therapy–Fatigue; LASA, Linear Analog Scale Assessment. This table contains data from all completed fatigue measurement instruments at each time point.

TABLE 3 Fatigue measures: least squares means (standard error)^a

Outcome	Baseline	8 Weeks	16 Weeks	24 Weeks	P ^b	
					Overall	24 Weeks
POMS-F score						
CoQ ₁₀	5.61 (0.45)	9.92 (0.67)	8.68 (0.71)	7.08 (0.71)		
Control	5.61 (0.45)	9.24 (0.70)	8.70 (0.74)	8.24 (0.79)		
Group difference	—	0.68 (0.93)	−0.02 (0.99)	−1.17 (1.03)	.473	.257
FACIT-F score						
CoQ ₁₀	40.0 (0.72)	33.7 (1.05)	34.7 (1.11)	37.6 (1.13)		
Control	40.0 (0.72)	34.9 (1.10)	36.6 (1.16)	37.6 (1.23)		
Group difference	—	−1.27 (1.43)	−1.91 (1.51)	0.07 (1.58)	.529	.965
LASA-Fatigue score						
CoQ ₁₀	2.44 (0.16)	3.92 (0.24)	3.96 (0.25)	3.08 (0.26)		
Control	2.44 (0.16)	4.12 (0.25)	3.69 (0.26)	3.48 (0.28)		
Group difference	—	−0.21 (0.33)	0.27 (0.35)	−0.41 (0.37)	.404	.267

Abbreviations: POMS, Profile of Mood States–Fatigue; FACIT, Functional Assessment of Chronic Illness Therapy–Fatigue; LASA, Linear Analog Scale Assessment.

^aLeast squares means are calculated at the mean level of each covariate.

^bP values are for differences between treatment groups; overall P value assesses differences at any time; 24-week P value assesses differences at 24 weeks.

points. This analysis again failed to reveal any indication of a CoQ₁₀ effect on fatigue, depression, and QOL.

Conclusions

Based on our data, there is no evidence to support the use of standard-dose CoQ₁₀ supplementation to ameliorate treatment-related fatigue in newly diagnosed women with breast cancer. Although fatigued patients without breast cancer were not specifically included in this study, there

are no compelling mechanistic data to suggest that these patients would respond differently to CoQ₁₀. In addition, this study was designed to limit and/or prevent fatigue among patients who were initiating adjuvant therapy. It was not targeted toward already-fatigued patients to try to reduce their symptoms. Given the results of this study, however, it does not seem likely that using CoQ₁₀ supplementation to target fatigued patients would result in better outcomes.

TABLE 4 Quality of life and depression, least squares means (standard error)^a

Outcome	Baseline	8 Weeks	16 Weeks	24 Weeks	P Values ^b	
					Overall	24 Weeks
FACT-B score						
CoQ ₁₀	111.3 (1.29)	105.0 (1.67)	108.3 (1.85)	111.9 (1.92)	.764	.577
Placebo	111.3 (1.29)	105.2 (1.73)	106.2 (1.89)	110.4 (2.07)		
Group difference	—	-0.16 (1.98)	2.10 (2.36)	1.46 (2.61)		
CES-D score						
CoQ ₁₀	12.0 (0.65)	13.0 (0.89)	11.6 (0.96)	11.6 (1.02)	.697	.632
Placebo	12.0 (0.65)	13.0 (0.93)	13.0 (1.01)	12.3 (1.11)		
Group difference	—	-0.05 (1.15)	-1.42 (1.28)	-0.69 (1.45)		

Abbreviations: FACT-B, Functional Assessment of Cancer Therapy–Breast Cancer; CES-D, Center for Epidemiologic Studies–Depression.

^aLeast squares means are calculated at the mean level of each covariate.

^bP values are for differences between treatment groups; overall P value assesses differences at any time; 24-week P value assesses difference at 24 weeks.

TABLE 5 Observed grade 3 and 4 toxicities

Toxicities	CoQ ₁₀		Placebo		Total
	Grade 3	Grade 4	Grade 3	Grade 4	
Allergic reaction	1	0	0	0	1
Anemia	1	0	0	0	1
Constipation	1	0	1	0	2
Dehydration	3	0	2	0	5
Diarrhea	3	0	2	0	5
Dizziness	1	0	0	0	1
Fatigue	1	0	3	0	4
Fever	2	0	1	0	3
Hot flashes	0	0	2	0	2
Hypotension	1	0	0	0	1
Ileus	1	0	0	0	1
Infection	5	0	2	1	8
Left ventricle dysfunction	0	0	1	0	1
Leukopenia	2	1	2	0	5
Neutropenia	6	6	2	2	16
Pain	1	0	4	0	5
Vomiting	1	0	1	0	2
Total	30	7	23	3	63

Each cell within this table contains the number of individual patients who experienced the listed grade 3 or 4 toxicity while enrolled in this trial. Row totals in the last column represent the number of unique patients who experienced each listed toxicity. Column totals given in the last row of the table represent the total number of occurrences of grade 3 and 4 toxicities and include patients who experienced more than one grade 3 or 4 toxicity.

Evaluation of dose-escalated CoQ₁₀ could be attempted, with an expectation of higher steady-state plasma CoQ₁₀ levels. However, the absence of any suggested benefit for the supplement in any of the patient subgroups examined in this trial indicates that newer approaches utilizing conventional or complementary

agents would probably be a better use of limited clinical research resources.

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