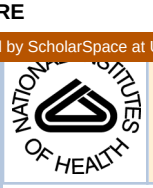

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Plasma Coenzyme Q10 levels and Postmenopausal Breast Cancer Risk: The Multiethnic Cohort Study

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Abstract

Background—Coenzyme Q10 (CoQ10) is a component of the mitochondrial electron transport chain and is considered an important cellular antioxidant. Decreased circulating CoQ10 levels have been reported in women with breast cancer, but evidence is limited. We examined the association of plasma CoQ10 levels with postmenopausal breast cancer risk using prospectively collected blood samples.

Methods—Pre-diagnostic plasma levels of total CoQ10 were measured among 160 incident postmenopausal breast cancer cases and 289 controls in the Multiethnic Cohort Study. Cases and controls were individually-matched on age, sex, ethnicity, study location (Hawaii or California), hormone replacement therapy use, date/time of specimen collection and hours of fasting. Logistic regression was used to compute odds ratios and 95% confidence intervals.

Results—Plasma CoQ10 levels were positively associated with breast cancer risk, overall (P = 0.04). The association was stronger after women diagnosed within one year of blood draw were excluded to eliminate possible preclinical cases (odds ratio for the highest versus the lowest tertile, 2.26; 95% confidence interval, 1.22-4.19; *P* for trend, 0.01).

Conclusions—Higher CoQ10 levels in postmenopausal women may be associated with increased breast cancer risk.

Impact—A potential role for CoQ10 in the development and progression of breast cancer has been postulated, but epidemiological evidence is lacking. Findings from this prospective cohort study add to the limited literature, indicating the potential positive association of circulating CoQ10 with postmenopausal breast cancer risk.

Keywords

Coenzyme Q10 postmenopausal breast cancer

Introduction

Coenzyme Q10 (CoQ10) is a component of the mitochondrial respiratory chain and is considered an important cellular antioxidant (1,2). Reduced CoQ10 availability or

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biosynthesis could lead to abnormal patterns of cell division and decreased apoptosis, factors that may increase the risk of malignancy (3), including breast cancer (4). Although the inverse association of CoQ10 with breast cancer risk may be direct through an influence on respiration in breast cancer tissue, it also may be indirect through reduced immune responsiveness (5,6) or reaction with cellular oxidants (2,7).

Epidemiological and clinical studies relating CoQ10 to breast cancer risk are limited. Folkers et al. (4) reported reduced levels of plasma CoQ10 among cancer patients, particularly in women with breast cancer. They also observed prolonged survival among eight cancer patients with diverse forms of cancer (including one with breast cancer) on therapy with CoQ10 (8). When 32 breast cancer patients were supplemented with CoQ10, other antioxidants and essential fatty acids, Lockwood et al. (9) observed partial tumor regression in four patients receiving 90 mg CoQ10 and complete remission in two patients receiving 300 to 390 mg/day CoQ10. Subsequently, Jolliet et al. (10) reported a significant positive correlation between levels of plasma CoQ10 and favorable breast cancer prognosis. Finally, Portakal et al. (11) examined CoQ10 levels in surgical resection tissue and surrounding normal tissue from 21 breast cancer cases. They found that CoQ10 levels were significantly lower in neoplastic breast tissue than in corresponding normal tissue, suggesting that CoQ10 may be consumed by reactive oxygen species in malignant cells. Despite the potential role for CoQ10 in the development and progression of breast cancer in these studies, epidemiologic evidence from large prospective studies is lacking.

Although the etiology of many postmenopausal disorders is attributable to a decline in ovarian function, menopause may also be associated with changes in CoQ10 and other antioxidants. Palan et al. (12) reported that postmenopausal women have significantly higher circulating levels of CoQ10 than do premenopausal women. They also found that postmenopausal women on hormone replacement therapy (HRT) had even lower circulating levels of CoQ10 than premenopausal women, suggesting that exogenous hormones may influence this molecule in plasma. The objective of the current study was to examine the association of pre-diagnostic plasma CoQ10 levels with postmenopausal breast cancer risk in a multiethnic population.

Materials and Methods

Study population and data collection

We conducted a nested case-control study of breast cancer within the Multiethnic Cohort Study (MEC), established in Hawaii and Los Angeles, California, from 1993 to 1996 (13). More than 215,000 adults aged 45-75 years completed a detailed questionnaire on diet and lifestyle. Five ethnic groups were targeted for inclusion in the cohort: African-Americans, Native Hawaiians, Japanese-Americans, Latinos, and non-Hispanic whites. A biospecimen subcohort was developed among MEC participants, primarily from 2001 to 2006, including 36,458 women who provided a blood (~94% fasting) specimen. Establishment of the Multiethnic Cohort and the biospecimen subcohort were approved by the Institutional Review Boards of the University of Hawaii and the University of Southern California.

Case ascertainment and control selection

Pre-diagnostic blood was collected and analyzed for total CoQ10 from 181 postmenopausal women with breast cancer who were identified through a 2007 linkage of the MEC with the Hawaii and California cancer registries. Data analyses were performed on 160 of these women with complete data on the adjustment variables described below. Two controls who were alive and free of breast cancer at the age of the case's diagnosis were randomly selected from the biospecimen subcohort and matched to each case by geographic location (Hawaii

or California), ethnicity, birth year (± 1 year), date (± 6 months) and time (± 2 hours) of specimen collection, fasting hours (0-<6, 6-<8, 8-<10, and ≥10 hours), and HRT use (current versus not current). Because of missing data for the adjustment variables, 31 controls were removed, leaving 289, with 129 cases matched to two controls and 31 matched to only one control. The median time from blood draw to date of diagnosis was 1 year and 5 months, with an interquartile range of 8 months to 2.5 years.

Laboratory assays

Plasma samples stored in vapor phase liquid nitrogen and never previously thawed were extracted using hexane after the addition of δ-tocopheryl laurate as an internal standard. The extracts were then stored at -80 °C for subsequent total CoQ10 analysis by HPLC (ThermoFisher, San Jose, CA) with pre-column electrochemical oxidation and post-column UV detection (14). Separation of analytes was performed on a Gemini C18 analytical column (Phenomenex, Torrance, CA) as described (14). Duplicate samples from QC plasma pools were included in each analysis batch yielding an inter-assay coefficient of variation of 7.6%. Extracted total CoQ10 samples are stable when stored at ≤ -10 °C. (14)

Plasma concentrations of tocophorols were analyzed using HPLC as previously described (15). Assays for sex hormones were performed at the Reproductive Endocrine Research Laboratory at the University of Southern California as described previously (16).

Statistical analysis

Conditional logistic regression, accounting for the matching criteria, was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). CoQ10 levels were categorized into tertiles based on the distribution of the overall study population (cases and controls) and a trend variable was created by assigning the median value of the appropriate tertile. The Wald χ^2 test was employed to evaluate the significance of the linear trend. The full logistic model was adjusted for body mass index (BMI), alcohol drinking, age at first birth, number of children, age at menarche, and age at menopause. Separate analyses were performed for subgroups defined by age, BMI, HRT use, alcohol consumption, tobacco smoking status, and plasma levels of tocopherols and sex hormones [free estradiol and sex hormone binding globulin (SHBG)]. When the match was broken for stratified analyses, unconditional logistic regression was employed with additional adjustment for the matching factors. Heterogeneity across subgroups was tested by a Wald test of cross-product terms. Analyses were repeated after excluding women (40 cases, 70 controls) diagnosed within 1 year of blood draw to eliminate possible preclinical cases. Partial correlations adjusted for the factors listed above were performed to assess whether CoQ10 levels were associated with plasma sex hormone and tocopherol levels. Covariate-adjusted means were used to compare plasma CoQ10 levels between current and not current HRT users. SAS software (SAS Institute, Cary, North Carolina) was used for all analyses. All tests were two sided, and $P < 0.05$ was considered statistically significant.

Results

Cases were similar to controls for most baseline characteristics, except that a somewhat greater percentage of cases than controls was nulliparous and had ever smoked tobacco or drank alcohol (Table 1). No significant differences were observed between cases and controls in levels of serum α-tocopherol (P = 0.63) or γ-tocopherol (P = 0.55).

Plasma CoQ10 had an inverse partial correlation with SHBG (r = -0.19, P = 0.007), and positive partial correlations with α-tocopherol (r = 0.25, P <0.0001) and γ-tocopherol (r = 0.33, P < 0.0001) levels among controls. Among cases, current HRT users had significantly

higher plasma CoQ10 levels compared to non-users (least-square means: 1097 ng/mL for HRT users, 916 ng/mL for non-users; P = 0.004).

Plasma CoQ10 levels exhibited a significant monotonic positive association with postmenopausal breast cancer risk (P = 0.04) (Table 2). The trend in odds ratios was stronger (P = 0.01) when 40 cases diagnosed less than one year after blood collection and their 70 matched controls were excluded to avoid the inclusion of women with preclinical disease. No statistically significant heterogeneity in the association of plasma CoQ10 with breast cancer risk was found by strata of BMI (normal weight versus overweight), plasma γ-tocopherol (above versus below median), or other potential effect modifiers (Table 3). Significant positive associations between CoQ10 and breast cancer risk were observed among normal weight women (BMI < 25) and women with γ-tocopherol levels below the median (Table 3). Because of the small number of current HRT users, we were not able to examine the association of CoQ10 with breast cancer risk by HRT use.

Discussion

Findings from this prospective cohort study add to the limited literature regarding the potential relation between CoQ10 and postmenopausal breast cancer risk. Plasma CoQ10 levels were significantly, positively associated with breast cancer risk, especially among women diagnosed at least one year after blood draw, suggesting that the inclusion of women with latent breast cancer may have somewhat attenuated the breast cancer-CoQ10 association.

Our results contrast with two previous studies (4,10) that reported lower levels of plasma CoQ10 in breast cancer patients compared to healthy controls. Folkers et al. (4) reported that 23% of breast cancer patients compared to 4% of cancer-free women had blood CoQ10 levels below 0.5 μg/mL (CoQ10 deficiency). Jolliet et al. (10) also found plasma CoQ10 levels were lower in 80 carcinoma patients than in healthy controls. These investigators did not have access to pre-diagnostic blood samples so circulating levels of CoQ10 may have been influenced by breast cancer and/or its therapy. In addition, participants in the study by Jolliet et al. (10) had a much wider age range (19 to 83 years) than in our cohort, including both pre- and post-menopausal women. It is possible that age or menopausal status may influence the association of breast cancer with levels of CoQ10, thus limiting our ability to directly compare findings from the present analysis with those of Jolliet et al.

Circulating CoQ10 may reflect different physiological conditions in postmenopausal breast cancer as compared to premenopausal breast cancer. A study by Palan et al. (12) reported that serum CoQ10 levels were higher among postmenopausal than among premenopausal women, suggesting that circulating steroid hormone or gonadotropin concentrations may influence plasma levels of CoQ10. The inverse association of CoQ10 with SHBG might partially explain the relation between CoQ10 and postmenopausal breast cancer, as higher SHBG concentrations are associated with reduced breast cancer risk (17). In contrast to Palan et al. (12), we found that plasma CoQ10 levels were higher among breast cancer cases who were current HRT users compared to non-users. Although HRT use is associated with an increased risk of breast cancer (18), its influence on the relation between CoQ10 and breast cancer risk requires further investigation.

Circulating CoQ10 may not be indicative of intracellular CoQ10. Increased circulating CoQ10 in aging humans may be a response to chronic inflammation and heightened systemic and/or tissue specific oxidation (19). The positive association between plasma γ-tocopherol and CoQ10 levels would be consistent with such a theory, as γ-tocopherol levels rise in response to inflammation (20,21), yet γ-tocopherol itself is thought to be an important

antioxidant that reduces cellular DNA damage resulting from nitrosative oxidation (21). In such a model, CoQ10 would not be causally related to postmenopausal breast cancer risk, but may represent a marker of adverse physiologic conditions. Clearly, the association of such markers with disease risk is complex and care must be exercised in their interpretation. The observation that CoQ10 was positively associated with breast cancer risk in individuals with low, but not high, γ-tocopherol levels deserves further investigation.

In conclusion, this study provides evidence suggesting a positive association of plasma CoQ10 levels with postmenopausal breast cancer risk. Although this investigation had some limitations, including the use of only one measure to assess circulating CoQ10 levels, the possibility that CoQ10 levels were not assessed during the relevant time period, and a relatively short follow-up time (75% of the cases were diagnosed within 2.5 years of blood donation), the results are nonetheless novel and biologically plausible. Prospective studies with a larger sample size and longer follow-up periods are needed to determine the potential role of CoQ10 in the etiology of breast cancer, as well as additional research into the physiologic regulation and function of circulating CoQ10.

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Table 1

Baseline characteristics of postmenopausal breast cancer cases and controls in the Multiethnic Cohort Study*

	Cases (N= 160)	Controls (N=289)
Age at blood draw (years), mean (SD)†	67.0 (7.7)	66.9 (7.7)
Fasting hours prior to blood draw, mean (SD)†	13.1 (1.7)	12.9 (1.9)
Current hormone therapy use, n (%)†	49 (30.6)	90 (31.1)
Ethnicity, n (%)†		
African-American	12 (7.5)	21 (7.3)
Japanese-American	69 (43.1)	120 (41.5)
Latina	26 (16.3)	48 (16.6)
Native Hawaiian	21 (13.1)	42 (14.5)
White	32 (20.0)	58 (20.1)
Number of children, n (%)		
0	22 (13.8)	30 (10.4)
1	9 (5.6)	28 (9.7)
2	46 (28.8)	76 (26.3)
≥ 3	83 (51.9)	155 (53.6)
Years of education, mean (SD)	13.8 (2.6)	13.7 (2.9)
Body mass index (kg/m^2), mean (SD)	25.6 (4.8)	25.5 (5.3)
Age at first childbirth, mean (SD)	23.1 (4.2)	23.8 (4.4)
Age at menarche, mean (SD)	12.9 (1.5)	13.0 (1.6)
Age at natural menopause, mean (SD)	48.6 (5.0)	49.7 (4.6)
Tobacco smoking status, n (%)		
Never	90 (56.3)	190 (66.0)
Former	52 (32.5)	71 (24.7)
Current	18 (11.3)	27 (9.4)
Mother or sister with breast cancer, n (%)	17 (11.1)	35 (12.5)
Alcohol use, n (%)		
Never	96 (60.0)	186 (64.4)
Ever, below users' median (3.4g/day)	31 (19.4)	53 (18.3)
Ever, above users' median	33 (20.6)	50 (17.3)
α-tocopherol (μg/mL), mean (SD)	17.0 (7.1)	17.5 (7.4)
γ-tocopherol (μg/mL), mean (SD)	1.39 (1.12)	1.48 (1.07)

*Cases and controls were matched on geographic location (California or Hawaii), ethnicity (African-American, Japanese-American, Latina, Native Hawaiian, or White), year of birth (± 1 year), date (± 6 months) and time (± 2 hours) of specimen collection, fasting status (0-<6, 6-<8, 8-<10, or ≥10 hours), and hormone replacement therapy use (current or not current).

†Matching variables.

Abbreviations: SD, standard deviation.

Table 2

Odds ratios and 95% confidence intervals (CI) for risk of breast cancer across tertiles of plasma coenzyme Q10 (CoQ10)

	CoQ10 tertiles[§] (ng/mL)	Cases	Controls[*]	Odds Ratio[†] (95% CI)	*P* for trend[‡]
All subjects	T1 (≤ 821)	45	105	1.00	
	T2 (821-1080)	54	95	1.53 (0.91-2.57)	
	T3 (≥ 1080)	61	89	1.77 (1.06-2.96)	0.04
Cases diagnosed ≥ 1 year after blood draw	T1 (≤ 821)	25	71	1.00	
	T2 (821-1080)	44	76	1.84 (0.99-3.42)	
	T3 (≥ 1080)	51	72	2.26 (1.22-4.19)	0.01

[*] Controls (n=289) were women matched to cases (n=160) on geographic location (California or Hawaii), ethnicity (African-American, Japanese-American, Latina, Native Hawaiian, or White), year of birth (± 1 year), date (± 6 months) and time (± 2 hours) of specimen collection, fasting status (0-<6, 6-<8, 8-<10, or ≥10 hours), and hormone replacement therapy use (current or not current).

[†] Estimated by conditional logistic regression with matched sets as strata, with additional adjustment for body mass index (continuous), alcohol drinking (never, <3.4, or ≥3.4 g/d), age at menarche (<13 or ≥13 years), age at menopause (<50 or ≥50 years), age at first birth (never, <25, or ≥25 years), and number of children (0-1, 2-3, or ≥4).

[‡] Linear dose–response in the logit of risk was estimated by a Wald test for CoQ10 modeled as a trend variable assigned the median value of the appropriate category.

[§] Medians of CoQ10 tertiles: T1, 668 ng/mL; T2, 934 ng/mL; T3, 1307 ng/mL.

Table 3

Odds ratios and 95% confidence intervals (CI) for risk of breast cancer across tertiles of plasma coenzyme Q10 (CoQ10) by strata of selected variables

	CoQ10 tertiles (ng/mL)	Cases	Controls	Odds Ratio* (95% CI)	*P* for trend†
Age at blood draw					
< 65 years	T1 (≤ 821)	18	45	1.00	
	T2 (821-1080)	21	40	1.34 (0.60-3.00)	
	T3 (≥ 1080)	29	39	1.91 (0.89-4.11)	0.10
≥ 65 years	T1 (≤ 821)	27	60	1.00	
	T2 (821-1080)	33	55	1.48 (0.77-2.84)	
	T3 (≥ 1080)	32	50	1.57 (0.78-3.12)	0.22
Body mass index					
< 25 kg/m^2	T1 (≤ 821)	22	63	1.00	
	T2 (821-1080)	27	58	1.48 (0.74-2.97)	
	T3 (≥ 1080)	31	42	2.61 (1.25-5.43)	0.01
≥ 25 kg/m^2	T1 (≤ 821)	23	42	1.00	
	T2 (821-1080)	27	37	1.17 (0.56-2.47)	
	T3 (≥ 1080)	30	47	1.07 (0.52-2.18)	0.90
Alcohol consumption					
Never drinker	T1 (≤ 821)	32	66	1.00	
	T2 (821-1080)	26	60	0.95 (0.50-1.83)	
	T3 (≥ 1080)	38	60	1.45 (0.77-2.71)	0.22
Ever drinker	T1 (≤ 821)	13	39	1.00	
	T2 (821-1080)	28	35	2.72 (1.13-6.54)	
	T3 (≥ 1080)	23	29	2.09 (0.84-5.21)	0.16
Tobacco smoking status					
Never	T1 (≤ 821)	28	69	1.00	
	T2 (821-1080)	32	65	1.18 (0.62-2.24)	
	T3 (≥ 1080)	30	56	1.39 (0.71-2.72)	0.33
Ever	T1 (≤ 821)	17	35	1.00	
	T2 (821-1080)	22	30	1.34 (0.56-3.23)	

	CoQ10 tertiles (ng/mL)	Cases	Controls	Odds Ratio* (95% CI)	*P* for trend†
	T3 (≥ 1080)	31	33	1.92 (0.82-4.52)	0.13
Sex hormone binding globulin					
< 42.1 nmol/L (median)	T1 (≤ 821)	21	31	1.00	
	T2 (821-1080)	15	35	0.58 (0.25-1.38)	
	T3 (≥ 1080)	28	40	1.10 (0.50-2.40)	0.63
≥ 42.1 nmol/L	T1 (≤ 821)	18	55	1.00	
	T2 (821-1080)	23	35	1.98 (0.88-4.46)	
	T3 (≥ 1080)	16	23	2.35 (0.91-6.07)	0.06
Free estradiol					
< 0.27 pg/mL (median)	T1 (≤ 821)	18	47	1.00	
	T2 (821-1080)	19	37	1.16 (0.51-2.61)	
	T3 (≥ 1080)	18	33	1.20 (0.51-2.78)	0.68
≥ 0.27 pg/mL	T1 (≤ 821)	21	38	1.00	
	T2 (821-1080)	19	33	1.18 (0.51-2.73)	
	T3 (≥ 1080)	26	29	1.70 (0.76-3.81)	0.19
α-Tocopherol					
< 15.58 μg/mL (median)	T1 (≤ 821)	25	58	1.00	
	T2 (821-1080)	29	46	1.56 (0.76-3.18)	
	T3 (≥ 1080)	26	39	1.82 (0.87-3.87)	0.11
≥ 15.58 μg/mL	T1 (≤ 821)	20	47	1.00	
	T2 (821-1080)	25	49	1.23 (0.59-2.56)	
	T3 (≥ 1080)	35	50	1.70 (0.82-3.52)	0.15
γ-Tocopherol					
< 1.07 μg/mL (median)	T1 (≤ 821)	24	68	1.00	
	T2 (821-1080)	22	43	1.56 (0.76-3.23)	
	T3 (≥ 1080)	28	40	2.39 (1.15-4.97)	0.02
≥ 1.07 μg/mL	T1 (≤ 821)	21	37	1.00	
	T2 (821-1080)	32	52	1.07 (0.52-2.22)	
	T3 (≥ 1080)	33	49	1.05 (0.50-2.18)	0.93

[*] Estimated by unconditional logistic regression, with adjustment for location (California or Hawaii), ethnicity (African-American, Japanese-American, Latina, Native Hawaiian, or White), age at blood draw (continuous), date/time of specimen collection (continuous), fast hours before blood draw (continuous), hormone replacement therapy use (current or not current), body mass index (continuous), alcohol drinking (never, <3.4, or ≥3.4 g/d), age at menarche (<13 or ≥13 years), age at menopause (<50 or ≥50 years), age at first birth (never, <25, or ≥25 years), and number of children (0-1, 2-3, or ≥4).

[†] Linear dose–response in the logit of risk was estimated by a Wald test for CoQ10 modeled as a trend variable assigned the median value of the appropriate category.