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Low plasma coenzyme Q10 levels and breast cancer risk in Chinese women

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Abstract

Background—Low circulating levels of Coenzyme Q_{10} (CoQ_{10}) have been associated with increased cancer incidence and poor prognosis for a number of cancer types, while a recent prospective study observed a positive association for CoQ_{10} with breast cancer risk.

Methods—We prospectively examined the association of plasma CoQ_{10} with breast cancer risk in a nested case-control study of Chinese women within the Shanghai Women's Health Study (SWHS). Pre-diagnostic plasma samples were obtained from 340 cases and 653 age-matched controls and analyzed for total CoQ_{10}.

Results—A borderline significant inverse association for breast cancer incidence with plasma CoQ_{10} level was observed using a conditional logistic regression model adjusted for age and age at first live birth, which became significant after elimination of cases diagnosed within one year of blood draw (p_{trend} = 0.03). This association was independent of menopausal status. Plasma CoQ_{10} levels were also observed to be significantly associated with circulating γ-tocopherol (r = 0.50; p < 0.0001) and with α-tocopherol (r =0.38; p < 0.0001) levels.

Conclusions—Circulating levels of CoQ_{10} were generally low in this population and the observed association with breast cancer risk may be limited to those women with exceptionally low values.

Impact—This study reports an inverse relationship between circulating CoQ_{10} and breast cancer risk, while the only other prospective study of CoQ_{10} and breast cancer to date found a positive association. Lower levels of CoQ_{10} in the SWHS population suggests that the two studies may not be contradictory and indicates a possible non-linear (U-shaped) association of CoQ_{10} with risk.

Introduction

Coenzyme Q_{10} (CoQ_{10}) was isolated and identified fifty years ago as an essential (rate-limiting) component of the mitochondrial electron transport system leading to ATP

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No potential conflicts of interest were disclosed.

production and is the only major lipid-soluble antioxidant synthesized by humans (1, 2). All mammalian cells are capable of synthesizing CoQ_{10} (or closely related molecules) in a complex biosynthetic pathway involving the mevalonate pathway (also responsible for cholesterol and dolichol synthesis) and tyrosine, in a process dependent upon eight essential vitamins and nutrients (3,4). Mitochondrial energy production is essential for eukaryotic cell survival and CoQ_{10} is a key molecule in all energy requiring processes, including proliferation, apoptosis, angiogenesis, and immune function (5–8), suggesting the potential for multiple roles in the initiation and progression of cancer. Despite the critical role of CoQ_{10} in many cellular functions, its potential relationship with cancer development and progression has not received appropriate attention. Epidemiological or clinical studies of plasma or tissue CoQ_{10} are rare in the literature and have involved limited numbers of subjects. Folkers, et al. (9), reported reduced circulating total CoQ_{10} levels in breast cancer (n=17) and myeloma (n=15) patients. Palan et al., (10) in a cross-sectional study (n=230), reported an inverse association between cervical intraepithelial neoplasia and cervical cancer with total circulating CoQ_{10}, as well as with α-tocopherol (αT) and γ-tocopherol (γT). Rusciani, et al. (11) reported a highly significant association between low plasma total CoQ_{10} levels and metastasis and progression in 117 melanoma patients. Recently, in the largest epidemiologic study to date of CoQ_{10} involving the Multiethnic Cohort, a positive association was observed for prediagnostic circulating total CoQ_{10} and breast cancer risk in postmenopausal women (12).

Administration of CoQ_{10} (as the oxidized quinone) to humans has been associated with a number of favorable clinical outcomes in the treatment of hypertension (13), heart failure (14), migraines (15), and myopathies associated with statin use (16). In the latter case there is growing concern for the long-term effects of statin use, resulting in decreased cellular CoQ_{10} synthesis and Boudroux, et al. reported a non significant increasing risk for breast cancer in women as a function of length of time on statins (17). Positive effects have been reported for CoQ_{10} in the treatment of breast cancer (18–20), however, these clinical studies were conducted on small numbers of patients and lacked adequate design.

Cellular and tissue levels of CoQ_{10} decrease with age, and cellular levels below a critical threshold are incompatible with life (21). In contrast, plasma levels of CoQ_{10} are reported by some to rise as a function of age (22), and are higher in postmenopausal women (23). Supplemental CoQ_{10} increases circulating α-T levels in animals (24) and humans (25), however, the determinants of circulating CoQ_{10} and its physiological regulation *in vivo* are unknown. The objective of the current study was to determine if an association exists between prediagnostic circulating CoQ_{10} and breast cancer risk among Chinese women from the Shanghai Women's health Study (SWHS).

Materials and Methods

Study Population and Data Collection

The Shanghai Women's Health Study (SWHS) is a cohort of approximately 75,000 adult Chinese women between the ages of 40 and 70 in Shanghai, China (26). Subject recruitment was initiated in June 1997 and completed in May 2000. The cohort is being actively followed through a combination of record linkage with the files collected in the Shanghai Cancer Registry and Vital Statistic Unit and a biannual home visit. Nearly all cohort members were successfully followed, with the response rates for first in-person follow-up being 99.8% (2000–2002), second 98.7% (2002–2004), and third 96.7% (2004–2007). All possible matches identified by record linkage were verified by home visits. Medical charts from the diagnostic hospitals were reviewed to verify the diagnosis, and pathological characteristics of the tumor were recorded. Breast cancer cases were defined as women for whom breast cancer was the first cancer diagnosis (ICD-9, code of 174).

Blood samples were collected from 56,900 subjects (76% of the cohort) during the baseline survey period. Over an approximately average 7.5 years follow-up, the number of incident breast cancer cases initially available for analysis was 386 with two controls for each index case (772) selected randomly from the group of cohort members who were free of cancer at the time of cancer diagnosis of the index case. The controls were matched to the index case by age (± 2 years), menopausal status at baseline (yes, no), date of sample collection (± 30 days), time of sample collection (morning or afternoon), time interval after the last meal (± 2 hours), and recent antibiotic use (yes, no). After exclusion of samples with inadequate plasma available, incomplete matching information, or analytical interference, 340 cases and 653 controls were used in the subsequent analysis. Cases without controls or controls without cases were deleted from the analysis.

Laboratory Assays

Plasma samples were stored at −75°C, thawed and then aliquoted in a dark room for analysis. Plasma samples were extracted using hexane after addition of δ-tocopheryl laurate as an internal standard. The extracts were then stored at −80 °C prior to subsequent analysis for total CoQ_{10} by HPLC (Model Spectra, ThermoFisher, San Jose, CA) with pre-column electrochemical oxidation (guard cell from ESA, Model 5020, Chelmsford, MA) and post-column UV detection at 275 nm (as described previously 12, 27). The separation was performed on a Gemini C18 analytical and guard column (150 mm × 2.0 mm, 3 μm and 4mm × 3.0mm, 10 μm, respectively; Phenomenex, Torrance, CA) with a mixture of sodium acetate trihydrate, glacial acetic acid, 2-propanol, hexane, and methanol. The range of inter-assay variability was 5 – 7 %. Plasma tocopherols were measured as described previously (28). Data for the distribution of CoQ_{10} levels among women was obtained from the current study and from another study (12) of CoQ_{10} and breast cancer utilizing the Multiethnic Cohort (MEC) performed by the same method in the same laboratory and provided by the authors of that study.

Statistical analysis

Conditional logistic regression, with matched sets as strata, was used to compute odds ratios (ORs) and 95% confidence intervals (CIs) whereby controls were matched to the index case by age, menopausal status at baseline, date of sample collection, time of sample collection, time interval after the last meal, and recent antibiotic use. CoQ_{10} levels were categorized into quintiles or quartiles based on the distribution of controls. The third quintile/quartile was chosen as the reference category to allow for a better comparison with the previous MEC study, in which the lowest tertile (median CoQ_{10} = 668 ng/ml) was used as a reference (12). In addition to matching variables, many potential confounding factors or effect modifiers have been obtained from survey or other studies (26,29). We conducted analyses to additionally adjust for age at first child birth, educational achievement, body mass index, regular physical activity (yes, no), number of full-term pregnancies, age at menarche, months of breast feeding, smoking status, and alcohol drinking. However, except for age at first live birth, adjusting for other covariates did not materially change the estimates. Stratified analyses were conducted by menopausal status and plasma concentration of γT (≤1948.9; >1948.9). Sensitivity analyses were conducted by excluding those whose blood samples were collected within one year of cancer diagnosis to reduce the effects possible pre-clinical cases. *P* values of <0.05 (2 sided probability) were interpreted as being statistically significant. Tests for trend were performed by entering the categorical variables as a continuous variable in the model. Statistical analyses were conducted using SAS statistical software (version 9.1; SAS Institute, Cary, NC).

Results

Baseline characteristics of patients and matched controls are shown in Table 1. Significant differences between cases and controls in the direction expected for this population were observed for education, age at menarche, age at first birth, months of breast feeding, and family history of breast cancer. Mean and median CoQ_{10} levels overall were slightly lower in cases compared to controls (Table 2), however the difference was not statistically significant. When stratified by menopausal status, postmenopausal women were observed to have approximately 20% higher average circulating CoQ_{10} levels compared to premenopausal women ($p = 0.07$ among controls).

As shown in Table 3, there was a borderline significant increased risk for all women in the lowest quintile of plasma CoQ_{10} compared to the third quintile. After exclusion for cases diagnosed within one year of blood draw to reduce possible overt pre-clinical cases, a significant inverse association for plasma CoQ_{10} with breast cancer risk was observed (p for trend = 0.03), with significantly increased risk for women in the 1st quintile (OR =1.90; 95% CI, 1.14–3.16) relative to the third quintile of plasma CoQ_{10}. We found plasma levels of CoQ_{10} significantly decreased with older age at first live birth ($p<0.01$). After including age at first live birth in the model, the OR (95% confidence interval) for the lowest plasma level of CoQ_{10} relative to the third quintile increased from 1.73 (1.07–2.80) to 1.90 (1.14–3.16) in the analyses excluding cases diagnosed within one year of blood draw. Stratification by menopausal status (Table 3) revealed similar trends by quartile with women in the lowest quartile of CoQ_{10} at elevated risk relative to the third quartile for both pre and postmenopausal women (p for interaction = 0.40). However, sample size became smaller and results did not reach significance in stratified analyses. Adjustment for tocopherols did not change the observed associations.

As shown in Figure 1, plasma CoQ_{10} levels were highly positively correlated with both plasma γT ($r = 0.50$; $p < 0.0001$) and αT ($r = 0.38$; $p < 0.0001$) levels. Circulating γT and αT levels were not correlated with one another. The distribution of values for plasma CoQ_{10} for the women analyzed in the SWHS is shown in Figure 2. Comparison data from a similar study of postmenopausal women in the MEC (12) are plotted for comparison. Significantly greater CoQ_{10} levels (approximately 60% higher) were observed in the MEC samples compared to the SWHS (means ± SD were 1,007 ± 387 and 631 ± 254 ng/ml, respectively, $p < 0.00001$). Comparing only post menopausal women, the median CoQ_{10} level in the MEC samples was 934 ng/ml compared to 633 ng/ml in the SWHS. In contrast, γT levels in women from the SWHS (median = 1.95 μg/ml) were nearly twice those observed for women in the MEC, where a median value of 1.07 μg/ml was reported (12).

Discussion

In the SWHS we observed a significant inverse association for low circulating CoQ_{10} with subsequent incidence of breast cancer for women whose breast cancer was diagnosed > one year after obtaining blood specimens with the highest risk associated with women in the lowest quintile of circulating CoQ_{10}. The results are consistent with previous reports of associations of low CoQ_{10} with increased risk for various cancers and their progression (9–11). However, a recent prospective study of postmenopausal women utilizing the MEC found a significant positive association between plasma CoQ_{10} and risk of breast cancer risk (12). That study (MEC) utilizing the same analytical laboratory as the current study found overall significantly higher levels of circulating CoQ_{10} in a multiethnic American population compared to the current SWHS study (Figure 2). The median CoQ_{10} for the reference tertile in the MEC study (668 ng/ml) was similar to the values for the SWHS cohort (536–629 ng/ml) where minimal risk was also observed. Significantly increased risk

for breast cancer was observed for the MEC study at CoQ_{10} levels >1,000 ng/ml, a level found in very few women in the SWHS. A possible explanation reconciling these opposing results is that women at either extreme of CoQ_{10} may be at increased risk for breast cancer. The Shanghai cohort encompasses the low end of what may be a U-shaped curve for CoQ_{10} and the MEC study (12) captures the high end (Figure 2). Both prospective studies appear consistent in that women with circulating CoQ_{10} levels in the range of 500–800 ng/ml have the lowest risk for developing breast cancer. It is unlikely that differences in sample collection or handling would account for any differences in CoQ_{10} levels between these two populations as all CoQ_{10} was oxidized to the stable quinone prior to analysis and measured as total CoQ_{10} by the same method and laboratory.

Because cells are capable of synthesizing CoQ_{10} endogenously, the question arises as to the source and physiological meaning of circulating CoQ_{10}. While the source and physiologic determinants of CoQ_{10} in the blood are unknown, the close relationship between CoQ_{10} and circulating tocopherols may provide some insight. The tocopherols were found to be highly associated with circulating CoQ_{10} levels, suggesting either a causal relationship or a common regulatory mechanism. The mechanism of regulation of circulating tocopherol levels is also unknown, however, tocopherols, particularly γT, are known to rise in response to inflammation (30, 31). The strong association between circulating CoQ_{10} and tocopherols suggests that CoQ_{10} level in the blood may also be mediated by systemic and/or localized inflammation (32). Increased release and/or retention of CoQ_{10} into the circulatory system may, like γT, be a response to processes such as inflammation, apoptosis, and cellular necrosis. Low circulating CoQ_{10} levels may represent inadequate cellular levels, low inflammation, enhanced excretion, and/or inadequate immune function. The immune system can participate in cancer etiology in two opposing manners (33, 34). Chronic inflammation with an overactive immune system can result in cellular DNA damage and the development of tumors over time, while an inadequate immune response can lead to decreased immune surveillance and allow tumors to progress and metastasize.

The SWHS population appears to be quite unique (Table 1) with few participants who were ever smokers (1.5% for cases, 2.9% for controls), ever drinkers (2.1% for cases, 2.9% for controls), and current hormone therapy use (3.8% for cases vs 1.4% for controls), indicating that the population is quite unique relative to Western societies, thus limiting comparisons with the results of Chai, et al. where considerably higher smoking, alcohol and HRT use were reported (12). Differences in diet and supplement use may account for the stronger association observed between γT and CoQ_{10} in the SWHS. Unlike studies in U.S. populations, where αT supplementation is more prevalent, no inverse association was observed between circulating γT and αT in women of the SWHS, which may account for the stronger association observed for both tocopherols with CoQ_{10}. In the study by Chai, et al. (12) the positive association between CoQ_{10} and breast cancer risk was strongest in women with low γT levels. In contrast, women in the SWHS were found to have generally higher γT levels and lower CoQ_{10} values (median γ-tocopherol of 1.95 μg/ml in the SWHS vs 1.07 μg/ml for the MEC women, 12). As was the case for CoQ10, all tocopherols were measured in the same laboratory and the lower levels of γT observed in the MEC are likely related to αT supplementation which significantly lowers γT, but does not affect CoQ_{10}.

In conclusion, the current SWHS study, with relatively larger sample size and longer follow-up time suggests an inverse association for plasma CoQ_{10} levels with breast cancer risk in Chinese women. The opposing relationships observed in the two prospective studies (SWHS vs the MEC), requires further research to verify the hypothesis that extreme levels of CoQ_{10} in the plasma are indicators of risk. Additional study into the physiologic significance and regulation of plasma CoQ_{10} and its relationship to tocopherols is needed. The present study does not address the role, if any, of supplemental CoQ_{10} in the prevention and treatment of

cancer. Future intervention studies that can assess the physiological effects of supplementation will be necessary to identify the likely cause and effect relationships and determine the possible therapeutic benefits or potential harm of supplementation of CoQ_{10}.

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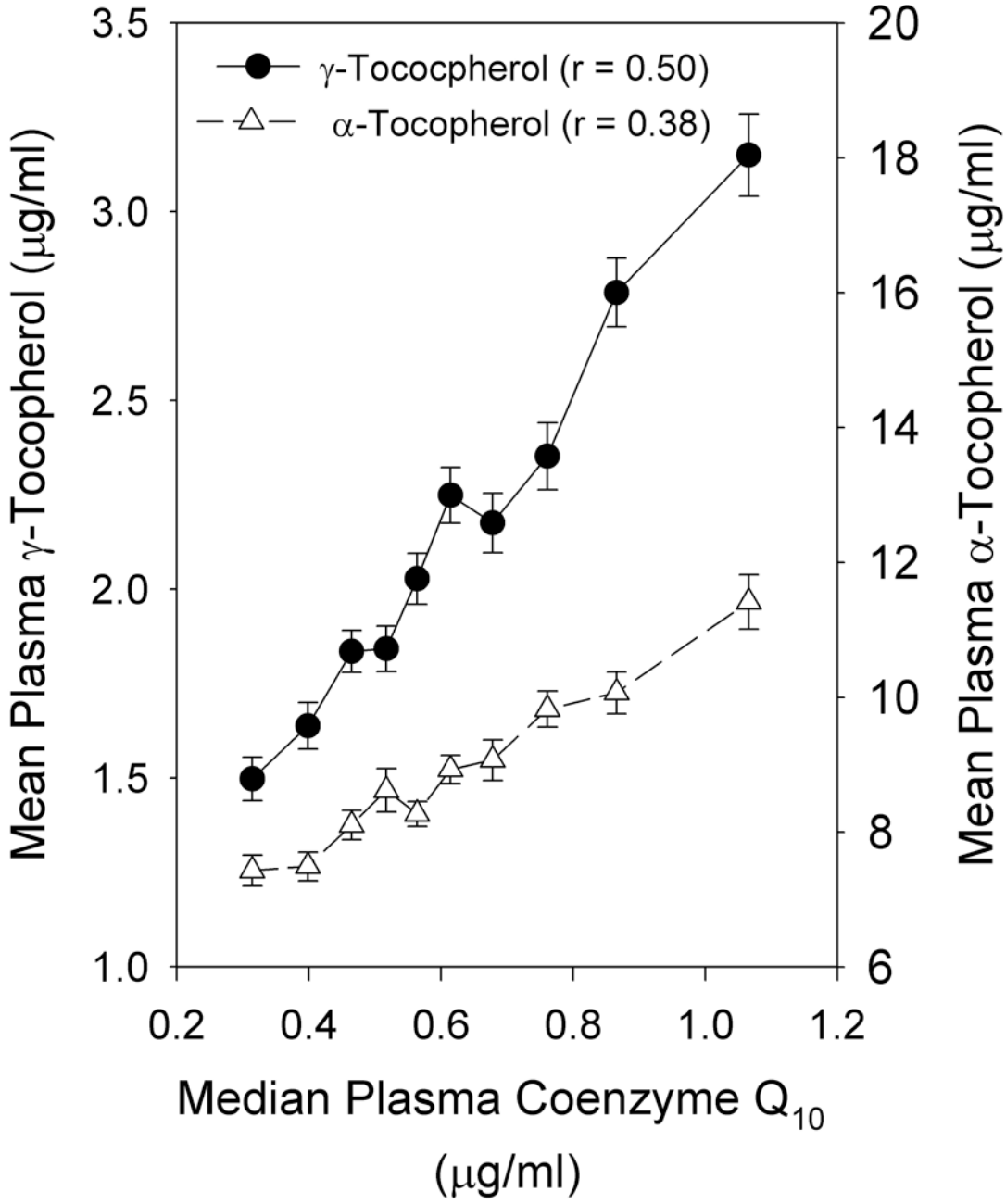

Figure 1.

Association of CoQ_{10} with tocopherols in plasma. All subjects (n=1,113) were stratified by plasma CoQ_{10} into deciles and α- and γ-tocopherol (mean ± SEM) plotted as a function of the median CoQ_{10} level for each decile. Correlation coefficients were calculated for the association of each tocopherol with CoQ_{10}.

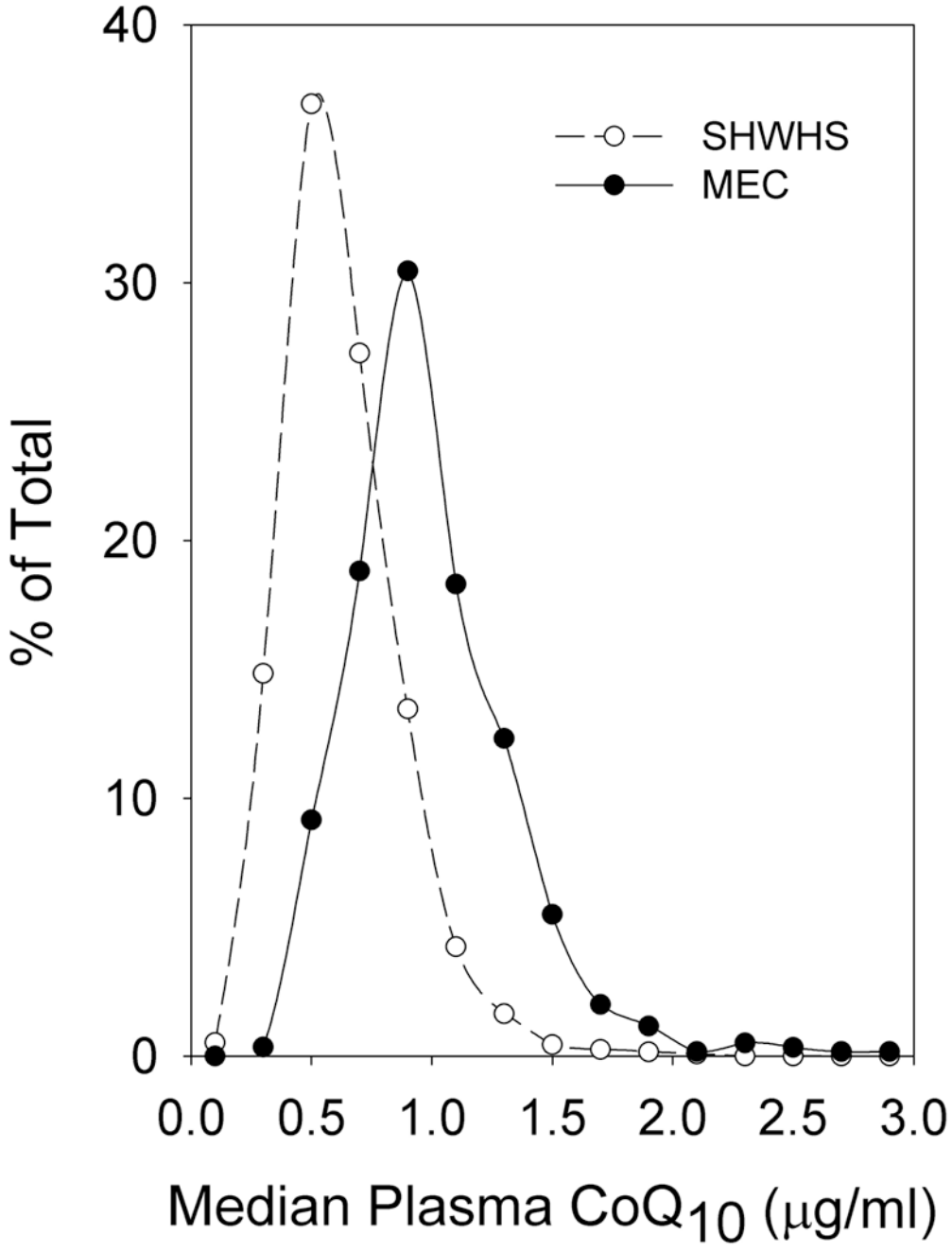

Figure 2.
Distribution of CoQ_{10} levels found in cases and controls of the Shanghai Cohort: comparison with postmenopausal women from the Multiethnic Cohort study of CoQ_{10} and breast cancer (12). The number of women with CoQ_{10} values were determined for each 0.2 μg/ml increase in plasma CoQ_{10} level and plotted as a percentage of the total number of women analyzed in the SWHS. For comparison, the distribution of plasma CoQ10 levels in women analyzed for a study of CoQ_{10} in the Multiethnic Cohort (12) are also shown.

Table 1

Characteristics of breast cancer cases and controls analyzed for CoQ_{10} in a nested case-control study within the Shanghai Women's Health Study (SWHS), 1997–2006.

Characteristics	Cases (n=340)	Controls (n=653)	P-value[#]
Age at blood draw (years), mean (SD)[*]	52.4 ± 9.0	52.4 ± 9.0	0.15
Current hormone therapy use, n (%)	13 (3.8)	9 (1.4)	0.04
Education, n (%)			<0.01
Elementary and under	52 (15.3)	151 (23.1)	
Middle school	121 (35.7)	267 (40.9)	
High school	116 (34.2)	168 (25.7)	
College and above	50 (14.7)	67 (10.3)	
Body mass index (kg/m^2), mean (SD)			
All Women	24.2 ± 3.6	24.4 ± 3.3	0.29
Premenopausal Women	23.4 ± 3.2	23.6 ± 3.1	0.48
Postmenopausal Women	25.1 ± 3.7	25.3 ± 3.3	0.54
Physically active, n (%)	122 (35.9)	222 (34.0)	0.67
Nulliparous, n (%)	15 (4.4)	24 (3.7)	0.29
Number of full term pregnancies, mean (SD)	1.7 ± 1.1	1.8 ± 1.1	0.05
Age @ first child birth, mean (SD)	26.3 ± 4.1	25.6 ± 4.2	0.01
Age @ menarche, mean (SD)	14.8 ± 1.8	15.0 ± 1.7	0.03
Months of breast feeding	13.7 ± 15.6	16.3 ± 18.4	<0.01
Smoking status, n (%)			0.39
Never	335 (98.5)	634 (97.1)	
Former	0 (0)	1 (0.1)	
Current	5 (1.5)	18 (2.8)	
Mother or sister with breast cancer, n (%)	14 (4.12)	10 (1.5)	0.01
Alcohol use, n (%)			0.71
Never	333 (97.9)	634 (97.1)	
Former	1 (0.3)	2 (0.3)	
Current	6 (1.8)	17 (2.6)	
Deaths, n (%)	40 (11.7)	20 (3.1)	<0.01
Postmenopausal, n (%)	165 (48.5)	320 (49.0)	0.06

[*] SD Standard deviation

[#] Conditional logistic regression model for categorical variables or *ANOVA* test for continuous variables

Table 2

Comparison of plasma Q10 (ng/mL) levels between breast cancer cases and controls, a nested case-control study within the Shanghai Women's Health Study (SWHS), 1997–2006.

Plasma CoQ_{10} concentration (ng/mL)	Cases	Controls	P-value
All women (340 pairs)			
Mean ± SD	605.4 ± 241.0	619.2 ± 185.4	0.25[a]
Median (25^{th}, 75^{th})	560.0 (435.0, 728.0)	597.0 (500.0, 714.0)	0.16[b]
All women with cases diagnosed > 1 year after blood draw (303 pairs)			
Mean ± SD	603.7 ± 242.8	622.9 ± 187.4	0.12[a]
Median (25^{th}, 75^{th})	553.0 (434.0, 739.0)	597.5 (502.5, 714.5)	0.09[b]
Premenopausal women (171 pairs)			
Mean ± SD	544.6 ± 223.5	554.9 ± 153.0	0.38[a]
Median (25^{th}, 75^{th})	508.0 (382.0, 649.0)	554.0 (450.5, 644.0)	0.13[b]
Postmenopausal women (169 pairs)			
Mean ± SD	667.0 ± 243.0	684.3 ± 192.9	0.45[a]
Median (25^{th}, 75^{th})	621.0 (494.0, 788.0)	649.5 (550.0, 789.0)	0.55[b]

[a] Paired test using log-transformed values for cases and the average of two matched controls.

[b] Paired Wilcoxon signed rank test for cases and the average of two matched controls.

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Table 3

Odds ratios (ORs) and 95% confidence intervals (CI) for risk of breast cancer associated with plasma level of Q10 and stratified by menopausal status, a nested case-control study within the Shanghai Women's Health Study (SWHS), 1997–2006.

		OR (95% CI) by quintile of plasma concentration of CoQ_{10}					
	Case-control pairs	**Q1[1]**	**Q2[1]**	**Q3[1]**	**Q4[1]**	**Q5[1]**	**P for trend**
				All women			
	340	1.55 (0.97–2.48)	1.14 (0.72–1.80)	1.00 (Ref)	1.11 (0.71–1.74)	0.97 (0.60–1.60)	0.09
				Women with cases diagnosed > 1 year after blood draw			
	303	1.90 (1.14–3.16)	1.41 (0.87–2.30)	1.00 (Ref)	1.15 (0.71–1.87)	1.13 (0.66–1.91)	0.03
		OR (95% CI) by menopausal status and quartile of CoQ_{10}					
		Q1[2]	Q2[2]	Q3[2]	Q4[2]	P for Trend	
				Premenopausal women[3]			
All	171	1.62 (0.91–2.89)	1.38 (0.78–2.44)	1.00 (Ref)	1.15 (0.65–2.02)	0.16	
>1 year	152	1.89 (1.01–3.54)	1.70 (0.91–3.16)	1.00 (Ref)	1.25 (0.68–2.32)	0.09	
				Postmenopausal women[3]			
All	169	1.35 (0.79–2.28)	1.04 (0.58–1.88)	1.00 (Ref)	0.96 (0.52–1.79)	0.24	
>1 year	151	1.71 (0.95–3.09)	1.14 (0.60–2.15)	1.00 (Ref)	1.15 (0.59–2.23)	0.14	

[1] 20^{th}, 40^{th}, 60^{th} and 80^{th} percentiles were 429.0, 536.0, 629.0, and 796.0 ng/ml, respectively for all subjects.

[2] 25^{th}, 50^{th}, and 75^{th} percentiles were 417, 537, and 665 ng/ml respectively for premenopausal women; and 517.5, 633, and 825 ng/ml respectively for postmenopausal women.

[3] P for interactions was 0.40.

A conditional logistic regression model was used whereby controls were matched to the index case by age, menopausal status at baseline, date of sample collection, time of sample collection, time interval after the last meal, and recent antibiotic use and additionally adjusted for age at 1^{st} live birth (continuous).