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Role of coenzyme q10 in breast cancer

Abstract

Background: Coenzyme Q10 (CoQ10) is a biological quinone compound that has two major physiological activities, as an antioxidant and as a redox component in the respiratory chain. Those CoQ10 activities among others may be of importance for the prognosis and treatment of breast cancer, which is the most commonly diagnosed cancer among women.

Objective: The purpose of this study was to conduct a literature review to identify and assess the evidence of the effect of CoQ10 for the treatment of breast cancer as a supplement, and to establish the relationship between CoQ10 levels and breast cancer.

Methods: In order to better understand the role of this coenzyme in breast cancer, an electronic literature search was conducted to identify all studies in which coenzyme Q10 was administered or measured in breast cancer patients.

Results: Six studies were included in this literature review. A relationship between CoQ10 levels and the risk of breast cancer was established. In those studies where patients were supplemented with a daily dose of 100mg of CoQ10, resulted in increased antioxidant levels, decreased cytokines plasma levels and reduced cancer biomarkers.

Discussion: CoQ10 acts as antioxidant in lipid peroxidation, helps regenerate antioxidant enzymes and decreases inflammation markers that contribute to proliferation, metastasis, cancer cell survival and angiogenesis.

Conclusion: The effectiveness of CoQ10 administration to improve the tolerability or prognosis of cancer treatments has not been fully evaluated and larger randomized clinical trials are needed to determine the optimum dose of CoQ10. However, the recommendation about the use of CoQ10 should not be considered as poor medicine practice, considering that it is safe, and the studies described in this review have some trends that favor the use of this supplement.

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Introduction

Breast cancer is the most commonly diagnose cancer in women, and is the second leading cause of deaths in women in the US. One in eight women will be diagnosed with breast cancer in their lifetime.[1] Each year it is estimated that over 220,000 women in the United States will be diagnosed with breast cancer and more than 40,000 will die.[1] According to the World Health Organization, breast cancer is the most common cancer among women worldwide, claiming the lives of women each year and affecting countries at all levels of modernization. Therefore, novel approaches to the management of breast cancer need to be developed.

Coenzyme Q10 (CoQ10) is biological quinone compound that is widely found in living organisms including yeasts, plants, and animals. There are a number of forms of Coenzyme Q, but Q10 is the major form found in humans and animals and has been studied the most. CoQ10 can also be found in a number of foods, such as mackerel, salmon, sardines, beef, soybeans, peanuts, and spinach. CoQ10 is widely used as a dietary supplement and two major physiological activities of it have been reported. One is the participation in oxidation reaction in the mitochondrial respiratory chain by enhancing the synthesis of ATP. The other is the antioxidant activity that appears with the reduced form only (ubiquinol).[2] As an antioxidant, CoQ10 blocks the action of free radical and activated oxygen species that can damage cells. Scientists also believe that CoQ10 may have an effect on the immune system by reducing cytokine levels.[3] Patients with cancer commonly try a variety of nontraditional treatments that fit the broad category known as Complementary and Alternative Medicine (CAM). Among the CAM therapies publicized by the popular press for cancer is CoQ10. There are many studies that suggest the use of (CoQ10) in cancer, showing some benefits with the use of it. However, studies of the use of CoQ10 in breast cancer are limited. The purpose of this study was to conduct a literature review to identify and assess the evidence of the effect of CoQ10 for the treatment of breast cancer as a supplement, and to establish the relationship between CoQ10 levels and breast cancer.

Methods

An electronic literature search was conducted to identify all studies in which coenzyme Q10 was administered to breast cancer patients or in which coenzyme Q10 levels were measured to determine the risk for developing breast cancer. The following databases were searched using EBSCO Host as the search engine: MEDLINE/PubMed, International Pharmacist Abstract (IPA), OVID, Cochrane Central Register of Controlled Trial, while EMBASE and Science Direct were searched using their own search engines. We limited our search for all databases from 2004 until February 2014, except for Science direct for which we expanded our search time period from 1999 to 2014. We performed the search using the terms and their pharmacological synonyms: breast cancer or tumor or biopsy and coenzyme Q10 or ubiquinone or co-enzyme Q10 or CoQ10 or Q10 or CoQ-10. During the search, studies were selected based on the following criteria:

human studies only, patients with breast cancer or at risk of developing breast cancer, females with age of at least 19years old, with or without mastectomy, with malignant or benign tumor(s). Study designs or article type such as randomized controlled trials, clinical controlled trials, case-reports and cohort-studies were included. Language of publication was restricted to English only. Studies were included in the synthesis of evidence if they used coenzyme Q10 as supplement for the treatment of breast cancer as mono therapy or as adjunct to standard of care. Also, Studies were included if they measured CoQ10 levels or clinical effects of CoQ10 supplementation. On the other hand, reviews were excluded once we identified cited studies that were relevant to our search. The search limiting criteria could not be applied to all databases, since each database provides different filters for setting such limits. Consequently, we manually reviewed each article, including only those articles matching the criteria pre-defined for the purpose of this review.

Results

From the literature search through the different databases, 14 studies were selected (Figure 1). These studies were conducted in Germany, London, India, United States, Iran, Japan, France, Turkey and China between 1999 and 2014. The types of studies selected were as follows: one nested case-control study, three randomized controlled trials, one clinical trial and one observational study. The ages varied among the studies from 19 to 83years. All of the studies were conducted in females. A dose of 100mg of CoQ10 was administered daily in those studies that were measuring the effect of CoQ10 supplementation. Table 1 shows the studies included in this review and evaluated either the levels or effects of CoQ10 in cancer patients.

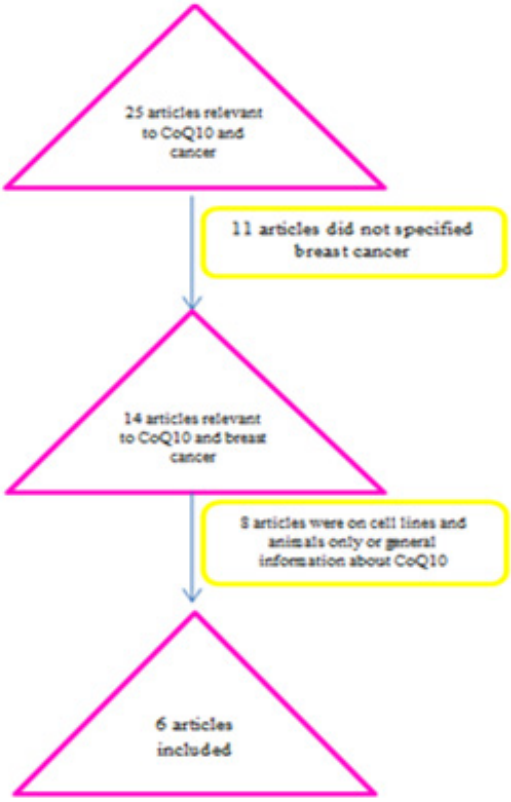

Figure 1 Flowchart of excluded studies.

Yuvaraj et al.[4] conducted a randomized controlled trial where the objective was to find if co-administration of CoQ10, Niacin and Riboflavin along with Tamoxifen (TAM) could augment the antioxidant (AO) status in postmenopausal women with breast cancer. Seventy eight treated postmenopausal women younger than 70years with resectable breast cancer were recruited. Blood samples were drawn at baseline, 45 and 90days. Treatment was Tamoxifen 20mg/day alone and Tamoxifen 20mg/day co-administered with CoQ10 100mg, Riboflavin 10mg and Niacin 50mg daily for 45 and 90days. In patients supplemented with CoQ10, Riboflavin and Niacin a significant decrease in lipid and lipid peroxidase were observed. A significant decrease in antioxidant enzymes in untreated and TAM treated group when compared to control subjects was observed. When supplemented with CoQ10, Riboflavin and Niacin these values were reverted back near to normal levels. There was no significant difference in the levels between 45 and 90days of treatment with CoQ10, Riboflavin and Niacin. Treatment with CoQ10, Riboflavin and Niacin for 45 and 90days significantly increased the non-enzymatic AO status to normal levels comparable to control subjects.

In a nested control case-control study by Cooney et al.,[5] the association of plasma CoQ10 with breast cancer risk on Chinese women was examined. For the analysis 340 cases and 653 controls were selected. Treatment was not specified. A not significant inverse association for breast cancer incidence with plasma CoQ10 level was observed when adjusting for age and age at first live birth, which became significant after elimination of cases diagnosed within one year of blood draw (ptrend=0.03). This association was independent of menopausal status. Plasma CoQ10 levels were significantly associated with circulating γ-tocopherol ($r=0.50$; $p<0.0001$) and with α-tocopherol ($r=0.38$; $p<0.0001$) levels. Portakal et al.[6] examined the relationship between oxidative stress and breast cancer development in tissue level to analyze antioxidant and to evaluate the consideration of CoQ10 as chemopreventing agent. Twenty one women with breast cancer (Invasive Ductal Carcinoma) were included. Cancer treatment was surgical therapy: Mastectomy with full dissection of axillary lymph nodes. Radiotherapy, chemotherapy, hormone therapy, radiotherapy plus chemotherapy, radiotherapy plus hormone therapy and combined treatment were used as adjuvant therapy. Table 1 shows the specific adjuvant pre-operative and post-operative therapy combinations used. Endogenous Co Q10 levels were decreased in tumor tissue ($p<0.001$). While, superoxide dismutase (SOD), mitochondrial superoxide dismutase (MnSOD), Catalase were significantly increased ($p<0.001$). Gluthathione peroxidase (GSH-Px) activity in tumor tissues was significantly higher than normal tissues ($p<0.001$). Malondialdehyde (MDA) levels were high in tumor tissue ($p<0.001$). There was a statistically significant correlation between both SOD activities ($r<0.79$; $p<0.001$). There is a linear correlation between MnSOD and catalase activities in both the normal and cancerous tissues ($r<0.57$; $p<0.05$). Jolliet et al.[7] determine the role of CoQ10 supplementation effect in a clinical trial. Two hundred women with breast cancer (malignant and non-malignant) were included. No treatment and no vitamin supplementation were administered. Plasma CoQ10 levels were measured. In healthy subjects, plasma CoQ10 range was 0.80-3.4μg/mL. Coenzyme Q10 levels were reduced in cancer patients and in women presenting non-malignant lesions. No significant difference between these 2 groups was found. When assessing CoQ10 levels in presence or absence of hormonal receptors in tumor tissue, a decrease in ubiquinone levels was observed in R- tissue when compared to R+ tissue. This observation was statistically

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significant (p<0.0001). CoQ10 levels are inversely associated with TNM classification. This measure had a statistically significant difference (p<0.05). Coenzyme Q10 levels were reduced in the presence (N+) or absence (N-) of locoregional cancerous adenopathy. There was no statistically significant difference between N+ and N- groups. Coenzyme Q10 plasma levels were further decreased with an increase in SBR grade (p<0.001). No correlation was found with age.

Table 1 Role of co enzyme Q10 in breast cancer

Reference	Design	Sample size	Types of breast cancer	Cancer treatment and dosage	Primary outcome measures	Results
Sachdanandam et al.[9]	Controlled clinical trail	N=210	Ductal invasive Lobular invasive	**Group I**: Healthy subjects **Group II:** Untreated breast cancer patient **Group III:** TAM alone **Group IV:** TAM+CoQ_{10} (100mg) daily for 45days **Group V:** treated with TAM+CoQ_{10} (100mg) daily for by 90days	CEA(µg/1) CA 15-3 (U/ml) IL-1β (i (pg/ml) IL-6 (pg/ml) IL-8 (pg/ml) TNF-α (pg/ml) VEGF (pg/m1) MPP-2 MPP-9	Untreated patients had serum cytokines levels significantly increased when compared to other groups. Patients who were supplemented with CoQio had serum cytokines levels significantly reduced compared to untreated patients and those with tamoxifen. The MMPs levels were found to be significantly increased in untreated patients when compared to healthy patients. In patients supplemented with CoQ_{10} is a significant reduction in pro-MMP2 and pro-MMP9 was observed when compared to patients taking only tamoxifen.
Yuvaraj et al.[4]	Randomized controlled clinical trail	N=202	Ductal invasive Lobular invasive	**Group I:** Healthy subjects **Group II:** Untreated breast cancer patient **Group III:** TAM 20mg alone **Group IV:** TAM 20mg, CoQ_{10} 100mg, Niacin 50mg, Riboflavin 10mg daily for 45days **Group V:** treated with TAM 20mg, CoQ_{10} 100mg, Niacin 50mg, Riboflavin 10mg daily for 90days	Antioxidant status in postmenopausal women with breast cancer.	A significant decrease in antioxidant enzymes in untreated and TAM treated group when compared to control subjects was observed. When supplemented with CoQ_{10} , Riboflavin and Niacin these values were reverted back near to normal levels.
Cooney et al.[5]	Nested control case-control study	N=993 340 cases 653 controls	Breast cancer	Not specified	Plasma CoQ_{10} levels	A not significant inverse association for breast cancer incidence with plasma CoQ10 level was observed when adjusting for age and age at first birth, which became significant after elimination of cases diagnosed within one year of blood draw. This association was independent of menopausal status.

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Table Continued..

Giridhar et al.[8]	Controlled clinical trail	N=210 42-helathy subjects 84-untreated patients 84-treated patients	Ductal invasive Lobular invasive	**Group I:** Healthy subjects **Group II:** Untreated breast cancer patient **Group III:** TAM 20mg alone **Group IV:** TAM 20mg, CoQ_{10} 100mg, Niacin 50mg, Riboflavin 10mg daily for 45days **Group V:** treated with TAM 20mg, CoQ_{10} 100mg, Niacin 50mg, Riboflavin 10mg daily for 90days	IL-1β (i (pg/ml) IL-6 (pg/ml) IL-8 (pg/ml) TNF-α (pg/ml) VEGF (pg/m1)	Cytokines levels were significantly increased in untreated breast cancer patients. Patients treated with Tamoxifen for more than a year had cytokines levels significantly decreased when compared to untreated patients. Patients that were supplemented with CoQ_{10}, Riboflavin and Niacin along with Tamoxifen had serm cytokines levels significantly reduced when compared to untreated patients and those taking Tamoxifen only.

Giridhar et al.[8] evaluated the prognostic significance of supplementing CoQ10, Riboflavin and Niacin along with tamoxifen to breast cancer patients. In this study 42 healthy controls, 84 untreated breast cancer patients and 84 breast cancer patients treated were included. Subjects were treated at baseline with Tamoxifen 10mg twice a day as monotherapy. Then, Tamoxifen 10mg twice a day co-administered with CoQ10 100mg, Riboflavin 10mg and Niacin 50mg for 45 and 90days. Serum cytokines levels of interleukin IL-1β, IL-6, IL-8, tumor necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF) were measured in this study. Untreated breast cancer patient (group 2) showed a significantly increased ($P<0.05$) levels of cytokines when compared to other groups. Cytokine levels were significantly reduced ($P<0.05$) in patients treated with tamoxifen (group 3), when compared to untreated patients. Subjects supplemented with CoQ10, Riboflavin and niacin along with tamoxifen for 45 and 90days had cytokine levels significantly reduced ($P<0.05$), when compared to groups 2 and 3. Sachdanandam et al.[9] evaluated the protective role of CoQ10 using a randomized controlled trial. For this study, 42 healthy controls, 84 untreated breast cancer patients and 84 treated breast cancer patients were included. They were 43 to 70years old with histopathology-confirmed breast cancer. Treatment was Tamoxifen for more than 1 year and Tamoxifen 10mg twice daily co-administered with CoQ10 100mg for 45 and 90days. Serum cytokines levels of interleukin IL-1β, IL-6, IL-8, tumor necrosis factor α (TNF-α), vascular endothelial growth factor (VEGF), Matrix metalloproteinase (MMP)-2, MMP-9, Tissue inhibitor of metalloproteinase (TIMP)-1, TIMP-2, Carcinoembryonic antigen (CEA) and Carbohydrate antigen 15-3 (CA 15-3) were measured in this study. Group 2 (untreated patients) had serum cytokines levels significantly increased ($p<0.001$) when compared to other groups. Group 3 (Tamoxifen for more than 1 year) had serum cytokines levels significantly reduced ($p<0.01$) when compared to group 2. Patients who were supplemented with CoQ10 for 45 and 90days had serum cytokines levels significantly reduced ($p<0.05$) compared to group 2 and 3. The MMPs levels were found to be significantly increased ($p<0.001$) in group 2 when compared to group 1 (healthy patients). In group 3 pro-MMP2 and pro-MMP9 levels were significantly reduced when compared to group 2. In patients supplemented with CoQ10 a significant reduction ($p<0.01$) in pro-MMP2 and pro-MMP9 was observed when compared to group 3. The serum levels of TIMP-1 and TIMP-2 were found to be significantly increased ($p<0.01$) in patients supplemented with CoQ10 when compared to group 3. The difference in levels of total cholesterol, free fatty acids and phospholipids was not statistically significant between group 2 and group 3.

Triglycerides levels were significantly increased ($p<0.001$) in group 3. Nevertheless, triglycerides levels were reverted back to near normal after 90days of co-administration with CoQ10. Plasma HDL-C levels were significantly reduced ($p< 0.01$) in Group 2 subjects as compared to Group 1. Plasma LDL-C and VLDL-C values were significantly elevated ($p< 0.001$) in Group 2 as compared to Group 1. The VLDL-C levels were significantly raised ($p< 0.001$) in Group 3 when compared to Group 2. In patient supplemented with CoQ10 VLDL-C levels were reverted back to near normal levels with no significant difference between 45 and 90days of supplementation. Group 1 had tumor markers (CEA and CA 15-3) levels significantly lower ($p<0.05$) than the other groups and lower than the cut off value (CEA 5µg/l and for CA 15-3 30U/ml). In patients supplemented with CoQ10 a significant reduction ($p<0.05$) in tumor marker levels was observed.

Discussion

This study was design to determine the relationship between CoQ10 levels and breast cancer, as well as to identify and evaluate the evidence for the outcomes obtained after supplementation of CoQ10 in breast cancer patients. A total of six studies were included and evaluated. Three articles provided data on the levels of CoQ10 and the relationship, if any with breast cancer. The other three articles targeted antioxidant and immunomodulation effects of the coenzyme Q10 as supplement to cancer treatment. There was a trend found by Cooney et al in which the lower the level of CoQ10, the higher the breast cancer risk. However, this inverse association was not significant.

When cases with less than year of being diagnosed were excluded, then a significant relation was observed. In contrast, a multiethnic cohort (MEC) study, including African Americans, Native Hawaiians, Japanese Americans, Latinas, and non-Hispanic white women, showed a significant positive association between CoQ10 levels and breast cancer risk. After stratifying the data for different patient characteristics, the only one that was statistically significant was for patients on the highest tertile of CoQ10 levels with tocopherol levels below the median. When comparing the multiethnic cohort with the Chinese cohort, the CoQ10 levels were lower in Chinese women.[5–10] This maybe due to the fact that the multiethnic cohort included only women from 45-75years old, which are postmenopausal, while Chinese cohort included premenopausal and postmenopausal Thus, CoQ10 levels vary depending on ethnicity and menopausal status. Jolliet et al.[7] also measured the CoQ10 plasma concentration in patients with malignant tumors and benign lesions. After contrasting ubiquinone plasma concentration in various prognosis groups of breast malignant tumors or benign lesions, there was a correlation between low CoQ10 levels and bad prognosis cancers. Women presenting higher TNM or SBR classification had lower levels of CoQ10. Likewise, hormone receptor negative subjects had lower levels of CoQ10. Nevertheless, CoQ10 levels were independent of whether the cancer was malignant or benign. Thus, these studies suggest that lower CoQ10 levels may be related to bad prognosis indicators based on TNM, SBR and hormone receptor status[7–10] Consequently, more studies are needed in order to determine if CoQ10 can be used as a prognosis indicator. There were some differences between these studies. Joliet et al.[7] did not have available a preclinical plasma level for the subjects, like MEC of Chinese cohort studies. The age range was wider (19-83years) in Joliet et al.[7] than in the multiethnic cohort, including both premenopausal and postmenopausal women. CoQ10 levels may be influenced by menopausal status.

A study by Palan reported that serum CoQ10 levels were higher in postmenopausal than in premenopausal women. The CoQ10 levels in women who use hormone replacement therapy (HRT) need to be studied, since this therapy may affect CoQ10 plasma levels.[7–9] Hence, there are studies indicating that low levels relate to breast cancer risk, while in another high CoQ10 levels are associated with breast cancer risk. There was a weak association found in CoQ10 levels, which were significantly decreased in tumor tissue, on the other hand, the levels were higher when compared to non-cancerous tissue from the same subject. However, the authors could not conclude if this was a consequence of higher antioxidant effect; resulting in more coenzyme consumption in tumor tissue, or because there was a low CoQ10 level in this tissue prior to developing the cancer. Even though, SOD, MnSOD, GSH-Px and Catalase increased significantly their activity in tumor tissue. Malondialdehyde (MDA), the lipid peroxidation marker, was high in tumor tissues. Therefore, this could reflect consumption of CoQ10 against the high peroxidative damage in tumor tissue. Furthermore, CoQ10 could protect lipids, proteins and DNA from oxidative chain reaction. In addition to its direct effect against lipid peroxidation, CoQ10 indirectly helps on the regeneration of vitamin E, which can interact directly with free radicals.[11] However, the levels of CoQ10 do not necessarily correlate to tochopherol levels. Cooney et al found a linear correlation of CoQ10 and tocopherol, while Jolliet et al found no correlation between CoQ10 levels and tocopherol levels, when comparing healthy subjects to patients with malignant and non-malignant breast tumors.[5,7] Tamoxifen (TAM) has been shown to be effective, not just as an adjuvant therapy after surgery, chemo or radiation therapy in early and advanced breast cancer cases, but also in chemoprevention in high-risk pre- and postmenopausal women. TAM is a non-steroidal anti-estrogen drug, which has led to an increase in both disease-free and overall survival of breast cancer patients after primary surgery.[9] Untreated and TAM treated breast cancer patients had lower antioxidant levels than control group. When patients were supplemented with CoQ10, Niacin and Riboflavin for 45 to 90days, their antioxidant levels were back to control subject antioxidant levels. The components of this combination supplementation provide the capacity to regenerate antioxidant enzymes such as SOD and GPx. These enzymes can act against free radicals before they damage biological macromolecules, such as lipids, proteins and DNA. CoQ10 is the only endogenously synthesized lipid-soluble antioxidant and protects membrane phospholipids and serum low-density lipoprotein (LDL) from lipid peroxidation. Also, CoQ10 can help regenerate vitamin E and vitamin C, resulting in higher antioxidant effect against lipid peroxidation and consequently DNA damage. It has been suggested that MDA, one of the lipid peroxidation products, can crosslink with DNA and proteins, causing mutations and non-functional proteins.[7]

Antioxidant depletion from plasma may be due to scavenging of lipid peroxidation in tissues as well as higher activity in cancer cells. This is consistent with what was reported by Portakal et al.[6] in which they observed a higher antioxidant enzymatic activity in tumor tissue when compared to same subject non-cancerous tissue.[6] Untreated and sole TAM-treated postmenopausal breast cancer patients were found to be oxidatively stressed as evidenced by the decreased antioxidant levels with increased lipid and lipid peroxide levels. It has been suggested that TAM can cause liver damage by oxygen radical production during its hepatic metabolism. Also, TAM may induce nitric oxide synthesis in breast tissue, which can produce radicals, resulting in oxidative damage. Thus, a higher enzymatic antioxidant activity will be expected in this tissue and may be the reason why a lower level of antioxidants was observed in these patients. However, the antioxidant effects measured in Yuvaraj et al.[4] were a result of the combination of CoQ10, Niacin and Riboflavin. Therefore, we cannot attribute the total antioxidant effect to ubiquinone alone.[4]

Patients on TAM had elevated triglycerides, VLDL and LDL. TAM is recommended to be use with caution in patients with hyperlipidemia. The group supplemented with CoQ10 for 90days, decreased triglyceride levels to near normal levels. This finding may be of benefit, when TAM therapy is indicated for patients having a history of hyperlipidemia. Another proposed mechanism for CoQ10 is modulation of the immune system. This immunomodulation effect was assessed by the Giridhar and Sachdanandam studies, by measuring the serum cytokine levels of interleukin IL-1β, IL-6, IL-8, tumor necrosis factor (TNF-α) and vascular endothelial growth factor (VEGF). Supplementation with CoQ10, Niacin and Riboflavin decreased significantly the levels of the cytokines. Cytokine levels were higher in untreated patients, while patients supplemented for up to 90days, were similar to healthy subjects. High levels of serum cytokines are associated with resistance to chemo-endocrine therapy and poor prognosis in breast cancer patients.[8] IL-1β is a pro-inflammatory regulatory cytokine, which plays a key role in breast cancer progression by regulating the functions of tissue and immune cells within the tumor microenvironment via expression of IL-1β receptors. IL-1β is known to induce the expression of a wide number of cytokines including angiogenic cytokine IL-8. IL-6 not only regulates VEGF expression, but also increases aromatase activity in

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both stromal cells and tumor cells. IL-6 promotes osteoclast formation and inhibits dendritic cell differentiation, thus facilitating metastatic growth, promotes cell migration by activating mitogen-dependent protein kinase pathway and inhibits apoptosis.[8]

TNF-α induces IL-6 production by macrophages and other cell types and conversely, IL-6 can inhibit TNF-α secretion by mononuclear cells.[8] IL-8 is an angiogenic chemokine, which plays an autocrine role in modulating survival and proliferation of tumor cells; its expression is enhanced by VEGF and both are modulated by hypoxia. Serum VEGF stimulates proliferation of tumor blood vessels and increases vascular permeability, which contributes to tumor cell extravasations and metastasis formation. High serum levels of VEGF reflect a large tumor mass or a rapid rate of angiogenesis due to greater vascular permeability.[8] Chronic inflammation in breast cancer promotes proliferation, apoptosis resistance, growth of cancerous cells and angiogenesis. Angiogenesis will provide the blood vessels needed to supply the blood that will transport oxygen and nutrients for the cancer cells to continue growing and proliferating uncontrollably. Macrophages have been found to attract carcinoma cells to intravasate into blood vessels and spread through the circulation; they secrete TNF-α, IL-10 or IL-8, altering the motility and invasion of breast cancer cells.[12] Serum cytokine levels were found to be very high among untreated breast cancer patients, the other groups cytokines levels were significantly low, including cancer free patients and those treated with TAM and CoQ10. These findings suggest that there is a relationship between CoQ10 levels and a decrease in cytokines levels such as IL-1, IL-6, IL-8, and TNF-α. Over expression of Matrix metalloproteinases (MMPs) has previously been associated with breast cancer progression.[13] It is generally assumed that the primary mechanism by which MMPs promote cancer spread is by degradation of the extracellular matrix, this consists of two main components: basement membranes and interstitial connective tissue, these facilitates the spreading of cancer cells through the endothelium.[12] Possible mechanisms by which MMPs contribute to cancer initiation or tumor cell growth include promotion of angiogenesis, activation of stimulating growth factors or their receptors, and inactivation of inhibiting growth factors.[14] Unlike MMPs, TIMPs have a role in the down-regulation of metastasis and angiogenesis, but indicate a possible involvement in tumor cell survival.[15] The levels of MMP-2 and MMP-9 were decreased, and TIMP-1 and TIMP-2 increased on CoQ10 supplementation, which shows the beneficial effect of CoQ10 supplementation to TAM therapy.[12]

Coenzyme Q10 levels are a powerful and independent prognostic factor that can be used to estimate the risk for pancreatic and melanoma progression.[16] Therefore, a study with more statistical power is needed in other to determine if CoQ10 may be used as a prognostic indicator as for pancreatic and melanoma progression. There is an in vitro study suggesting a significant negative correlation between CoQ10 and H2O2 as well as a significant decrease in MMP-2 activity in MCF-7 (a renowned model of cancerous breast ductal epithelium) cells. MMP-2 is a marker and has the same effects as other MMPs with respect to growth, progression and metastasis in addition to deregulated angiogenesis. As a result, MMPs have come to represent important therapeutic and diagnostic targets for the therapy and diagnosis of human cancers in which their increase presages invasive phenotypes.[17] Elevated CA 15-3 and CEA levels are directly related to tumor burden and are independent prognostic factors for breast cancer.[16] Sachdanandam demonstrated that group III patients treated with CoQ10 along with TAM for 45days and 90days, there was a significant reduction ($p<0.05$) in tumor marker levels of CEA and CA15-3.15 Decrease in tumor marker levels prove the valuable effect of CoQ10 supplementation to breast cancer patients, a reduction in marker level is suggestive of a biochemical response, presenting better disease stabilization and survival as well as an improved quality of life.[18] This review reinforces the fact that CoQ10 studies in breast cancer patients are lacking. This study adds to the foundation of evidence in order to develop the proper hypothesis for randomized controlled clinical trials in order to demonstrate the safety and effectiveness of coenzyme Q10 as a supplement to adjuvant and neoadjuvant breast cancer therapy or even as prevention. Nevertheless, more studies are needed in breast cancer patients to have a better understanding of the antioxidant and immunomodulation mechanisms of CoQ10. This literature review had some limitations. First, there are a limited number of studies relating CoQ10 with breast cancer, especially in humans. Second, most of the studies evaluating CoQ10 use it in combination with niacin and riboflavin. Therefore, the antioxidant effects cannot be attributed to CoQ10 alone. Only one study used coenzyme Q10 alone as supplement of cancer therapy. Third, the age range maybe to broad. Consequently, more studies are needed to determine the effect of postmenopausal versus premenopausal status, since it may affect the CoQ10 levels. Also, the effect of Hormone Replacement Therapy would be important in evaluating the role of CoQ10 in breast cancer, since it could affect its level. Fourth, the sample size for most studies is small, decreasing the power for their results. It would be difficult to extrapolate these results, since most of these studies only consider cancer therapy with tamoxifen and there is no data considering chemotherapy. The studies should control for diet, ethnicity, environment and genetic cofounding effects. According to the studies evaluated, it is not clear for which specific type of breast cancer will the supplement of CoQ10 will be more beneficial. Although, it was shown that could be more helpful in cancer patients with bad prognosis indicators, untreated or treated with TAM alone patients, in which could increase the antioxidant activity levels and decrease the inflammatory markers that promote cancer progression.

The rationale for the use of CoQ10 as a therapeutic agent is based upon its fundamental role in mitochondrial function, cellular bioenergetics as well as antioxidant and immunomodulation effect. This statement is reinforced because CoQ10 has an excellent safety record and is well tolerated at high doses over long periods with limited side effects 2. CoQ10 plasma levels should be monitored during clinical studies using different doses as a supplement for standard breast cancer treatment. This will facilitate the interpretation of the results of the treatment. Oral CoQ10 supplement may be administered in persons with low levels. Unfortunately, the studies included do not measure consistently CoQ10 levels in plasma, thus the relationship of clinical response to CoQ10 concentration in plasma frequently are not tangible. There is a need for large multi-centre, monitored double-blind placebo-controlled trials, where the plasma CoQ10 levels should be carefully monitored, in order to investigate efficacy, since safety has been proven.

Conclusion

The effectiveness of CoQ10 administration to improve the tolerability or prognosis of cancer treatments has not been fully evaluated and larger randomized clinical trials are needed to determine the optimum dose of CoQ10. However, the recommendation about the use of CoQ10 should not be considered as poor medicine practice, considering that it is safe, and the studies described in this review have some trends that favor the use of this supplement.

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Conflict of interest

Author declares that there is no conflict of interest.

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