Coenzyme Q10 in breast cancer care

Ali Tafazoli*

Introduction: Breast cancer (BC) is the most common type of cancers with high rates of morbidity and mortality. By now numerous medical approaches are available for treatment of BC including chemotherapies, radiation and surgery. These are accompanied by several complications like partial effectiveness, fatal adverse effects and high cost. Numerous studies in recent years tried to find safe and effective alternatives. A promising candidate is coenzyme Q10 which is an antioxidant that can target the mechanisms of BC tumor progression. Methods & results: In this systematic review via PubMed searching, sparse but promising findings were classified about the successful application of this compound as an adjunct in prevention and treatment of BC and its comorbidities with some contradicting data about its null effect. Discussion & conclusion: According to the results, further well-designed clinical studies with dose optimization are now required to stratify the role of this supplement in current BC regimens.

Breast cancer (BC) is the most common type of cancer affecting women, all over the world. The incidence of this malignancy is increasing especially in developing countries. Considering the high prevalence of BC, which is also occurring in men, it is shocking to know that the 5-year survival rate in metastatic cancer cases can be lower than 30%. Therefore, identification of risk factors and determination of preventive measures are extremely important. Numerous predisposing factors for BC have been proposed till now and dietary factors including certain deficiencies are among the top ones. As a consequence, supplementation with various nutraceuticals has been the subject of many scientific and clinical investigations.

Coenzyme Q10 (CoQ10) or ubiquinone is a well-known inborn antioxidant with different biologic activities like immune boosting, radical scavenging and DNA protection [1]. There is evidence that shows an association between CoQ10 deficiency and several kinds of cancers [2]. Therefore, administration of CoQ10 has been tried in some studies to prevent or treat cancers. These studies revealed promising but controversial results. There are limited and sparse data that show beneficial effects for CoQ10 supplementation in management of BC [3]. These positive but questionable evidences have produced a trend among clinicians for administration in patients for consumption of CoQ10 in recent years [4]. Accordingly, major indications of CoQ10 use have been BC prevention, improving efficacy of cancer therapy and controlling adverse effects of common therapies [3,5]. The aim of this review is gathering and categorization of these facts to evaluate our current knowledge about this issue and provide a better foundation for future anticancer research to save more BC patients.

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**Materials & methods**

For classification, clarification and presentation of the available scientific evidence about use of CoQ10 in management of BC in this systematic review, one of the most accredited scientific databases, PubMed, was explored with keywords (MeSH terms) ‘coenzyme Q10’ and ‘breast neoplasms’. The search order was (“Breast Neoplasms”[Majr]) AND “coenzyme Q10” [Supplementary Concept]. Only journal articles were acceptable for this review. There was no language restriction in our methodology but all articles had English abstracts. According to low number of search results, no time limit was planned for the included articles. Twenty four journal articles were yielded. The major eligibility criteria were randomized controlled trials and quasi-randomized trials with human subjects and choosing the articles were in adherence to the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ guidelines as much as possible. Also in order to provide a more comprehensive review, the rest of journal articles were mentioned under separate titles. A flow diagram of data selection is presented in Figure 1. Due to lack of adequate number of clinical trials and the fact that different products, different doses and different outcomes had been assessed in each study, implementation of a meta-analysis is considered to be misleading in this paper. Instead we tried to classify the studies in a table to facilitate the comparison and evaluation.

**Results**

In the search results, there were in vitro, in vivo (animal) and clinical findings about the role of CoQ10 in development, prevention and treatment of BC. We captured two in vitro studies on BC cell cultures and one animal study with the search process. Another study used isolated cancerous tissues obtained from radical mastectomies. Of 24 yielded journal articles, 10 were related to randomized controlled trials but these articles were derived from only three distinct clinical trials. The cumulative number of enrolled participants was 421, including 234 subjects in intervention groups and 187 controls. The assessed outcomes in these studies were survival, tumor regression and relapse, disease progression and tumor invasion, quality of life, mood, fatigue and performance status, and adverse effects. Among other clinical studies, there were two journal articles related to an uncontrolled trial with 32 participants, two epidemiologic cohort studies (500 cases and 942 controls) and a supplementation-trend survey with 160 examinees. These studies were classified in separate categories for the review.

**Discussion**

- **CoQ10 deficiency as a risk factor**

Examination of breast tissue samples of BC patients shows that concentrations of CoQ10, as a marker of body antioxidant capacity, are significantly lower in cancerous tissues compared with the surrounding normal tissues. Counteraction of the destructive effect of reactive oxygen species on cellular and DNA integrity has been suggested for CoQ10 mechanism of action in this issue [6].

An inverse association between CoQ10 levels and BC has been proposed in case-control studies [7]. In a prospective nested case-control study of Chinese women within the Shanghai Women’s Health Study with 340 BC cases and 653 controls, researchers found an inverse association between circulating plasma CoQ10 levels and BC incidence, independent of menopausal status [2].

Such findings have made the researchers to suggest CoQ10 supplementation as a preventive approach against BC. Although there are contradicting observations, these findings are supported by some preclinical (in vitro and animal) studies as well as clinical ones.

- **In vitro evidence**

Modulation of intracellular oxidative damages has been introduced as the major mechanism of action for CoQ10 on BC pathophysiology. Matrix metalloproteinase (MMP) has a major role in pathogenesis of certain diseases including cancers. It facilitates cancer cell division, proliferation and migration. Among such enzymes, MMP-2 is a well-known predicting marker of growth, progression, metastasis and angiogenesis of solid tumors. These are more frequently produced and activated in presence of reactive oxygen species. Therefore, antioxidants have the potential to hinder this process. Unfortunately the majority of current antioxidants are hydrophilic with lack of adequate exposure in the required sites of action. From a few natural lipid-soluble antioxidants, CoQ10 is the only one which is available mostly in the reduced and functional form. It has been shown in an in vitro study on Michigan Cancer Foundation-7 (MCF-7) BC
Figure 1. Flow diagram depicting the study selection and categorization process for ‘Coenzyme Q10’ and ‘breast cancer’ search results.

RCT: Randomized controlled trial.

Cell lines that coincubation of CoQ10 can significantly decrease intracellular H$_2$O$_2$ content and MMP-2 activity in a dose-dependent manner. Considering the role of these molecules in the process of tumor-related invasion and metastasis, this observation revealed the importance of CoQ10 presence and levels on inhibition of cancer development and possibility of boosting the effect of BC chemotherapy.[1] Besides increasing the effectiveness of BC chemotherapy, CoQ10 showed protective effects against some of life-threatening adverse effects of both cytotoxic and hormonal medications for treatment of BC. Considering doxorubicin as a common chemotherapy for BC, a considerable number of patients will be affected by cardiomyopathy and consequently congestive heart failure via reactive oxygen species in myocyte...
mitochondria that are produced by this drug. CoQ10 can save mitochondrial damage by reactive oxygen species and prevent doxorubicin-induced cardiotoxicity. However, these protective effects can theoretically compromise the effectiveness of oxidative chemotherapies on breast tissue. This theory was examined in an in vitro study on MDA-MB-468 and BT549 BC cell lines with concurrent exposure to doxorubicin and different CoQ10 concentrations. The results showed that CoQ10 had no inhibitory influence on apoptotic, antigrowth and anticolonization effects of doxorubicin at any doses. This finding provided the chance for implementation of clinical studies in patients under doxorubicin therapy [8].

● In vivo evidence

In an animal study with mammary carcinoma model induced by dimethyl benz(a)anthracene, oral administration of CoQ10 with the dose of 40 mg/kg body weight per day restored lipid peroxidation and tissue antioxidants to near-normal status. This combination also demonstrated an antitumor activity with increased expression of tumor suppressor genes and antiproliferative effects [9]. These characteristics make the CoQ10 an acceptable subject for BC treatment clinical studies.

● Clinical studies

Several studies with human subjects, including randomized clinical trials, have evaluated the effect of CoQ10 supplementation for management of BC. Some of these evaluated the direct effect of CoQ10 on the tumor tissue and disease progression including exploration of tumor markers. As a collateral outcome, the preventive influence on chemotherapy complications and toxicities like dyslipidemia, were also assessed in concurrent studies. Some others evaluated the potential benefits of this supplement on severity of the cancer comorbidities and quality of lives (Table 1).

In an early uncontrolled clinical study on 32 high-risk BC patients with tumor invasion to adjacent lymph nodes, daily supplementation with a combination product consisting essential fatty acids (1.2 g linoleic acid, 3.5 g n-3 fatty acids), antioxidants (58 mg β-carotene, 2800 mg vitamin C, 2500 IU vitamin E and 385 μg selenium) and 90 mg of CoQ10, added to medical and surgical treatment, resulted in apparent tumor remission in six of them between ages 48 and 82 years. Other desirable outcomes were reduced opioid use for pain, prevention of distant metastases and no deaths after 24 months. Increasing the CoQ10 dose to 300–390 mg in two cases was associated with resolution of tumor residue without any metastases after several more months. The patients reported feeling of well being with better quality of life and excellent compliance [10–12]. Further follow-ups exhibited outstanding 5-year survival rates of 50% for high-risk (metastatic) patients and 90% for lower-risk patients after 10 years [23].

In another clinical trial, a group of 42-aged and socioeconomic-matched healthy women were compared with a group of 84 BC patients at four different statuses regarding therapy with tamoxifen 10 mg twice daily and supplementation with a combination product consisting 100 mg CoQ10, 10 mg riboflavin and 50 mg niacin. By checking markers of disease progression like carcinoembryonic antigen and carbohydrate antigen 15-3, observations revealed that the supplement had caused significant reduction of tumor markers in a time-dependent manner [13]. Also, augmentation of poly (ADP-ribose) polymerase activity and antiangiogenic factors and suppression of RASSF1A DNA methylation and proangiogenic

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population characteristics</th>
<th>Coenzyme Q10 oral dosage</th>
<th>Indications</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lockwood et al. (1994)</td>
<td>Typical breast cancer patients classified high risk because of tumor spread to lymph nodes; aged 32–81 years</td>
<td>90,300, 390 mg/day</td>
<td>Adjuvant therapy</td>
<td>[10–12]</td>
</tr>
<tr>
<td>Premkumar, Sachdanandam, Yuvaraj et al. (2007–2009)</td>
<td>Histopathology-confirmed postmenopausal breast cancer patients at different stages of chemotherapy; aged 43–70 years</td>
<td>100 mg/day</td>
<td>Adjuvant therapy; controlling adverse effects of chemotherapy</td>
<td>[13–20]</td>
</tr>
<tr>
<td>Lesser et al. (2013)</td>
<td>Newly diagnosed breast cancer women scheduled for adjuvant chemotherapy; aged 28–85 years</td>
<td>300 mg/day</td>
<td>Controlling cancer comorbidities (fatigue)</td>
<td>[21]</td>
</tr>
<tr>
<td>Iwase et al. (2016)</td>
<td>Breast cancer patients with cancer-related fatigue undergoing chemotherapy; aged 29–70 years</td>
<td>30 mg/day</td>
<td>Controlling cancer comorbidities (fatigue)</td>
<td>[22]</td>
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markers have been reported with this supplement in the study cases that shows tumor suppression in every aspects with better prognosis and treatment efficacy for the patients [14–16].

Besides anticancer actions of CoQ10-containing supplements, several beneficial effects have been proposed on BC comorbidities. Enhancement of antioxidant defense system against BC-related oxidative stress with combination of CoQ10, niacin and riboflavin, is one of them [17]. As mentioned, such supplements can also be useful in management of toxicities related to BC hormonal or cytotoxic therapies. Liver injury and dyslipidemia induced by long-term tamoxifen administration has been corrected with the same product [18,19]. In a randomized clinical trial on 59 BC patients with cancer-related fatigue, participants were divided in two groups of receiving either an oral supplement containing CoQ10 and L-carnitine daily or only regular care for 3 weeks. Evaluation of parameters like worst level of fatigue, current feeling of fatigue and global fatigue score on the first and last day showed a significant improvement in moderate to severe cancer-related fatigue with this product [20].

Although general findings of these studies were promising, there are few evidences for a null effect or even adverse associations of CoQ10 and BC which are stated in the following section [21,24].

### Conclusion

Numerous preclinical studies have demonstrated the potential benefits of CoQ10 as an anticancer agent against solid tumors including BC. But it seems that the amount of clinical evidence about effectiveness of CoQ10 in management of BC is still not enough, because considerable number of results and consequently provided journal articles are derived from few individual clinical trials in this field. Also, those clinical studies had severe defects in their designs and evaluations. However most of such studies demonstrated an acceptable efficacy for CoQ10 supplements in ‘combination’ products, none of them were able to stratify the effect of sole CoQ10 on breast malignancies. It should be noted that these beneficial effects can be due to presence of other components or a synergistic resultant of all ingredients. Indeed a rare article, in which the author claimed of using only CoQ10 in BC patients with restriction of participants to consume other supplements, was very suspicious regarding validity of the data [20]; because the year of publication, number of participants and characteristics of patients were exactly the same as those enrolled by a group of researchers including the author in another study that had used combination supplements [14].

Adding to that, there are also controversial findings about the potential benefits and effectiveness of CoQ10 supplementation in BC. In a major randomized, double-blind, placebo-controlled study on this topic, 236 BC women eligible for adjuvant chemotherapy were randomized to receive either 100 mg CoQ10 three-times daily or placebo both with vitamin E as a liquid carrier for improvement of CoQ10 oral absorption. Supplementation was begun on early days of start of chemotherapy and continued for 24 weeks. Evaluation of blood samples and quality of life parameters at baseline, during and at the end of trial, presented no significant difference between groups in mood, fatigue or functional assessments; even though the levels of blood CoQ10 were significantly increased in the intervention group. The authors stated that these findings could not negate the possible effects of CoQ10 at higher doses, which had been tolerated acceptably in other studies. Unfortunately, despite the well-designed structure of this study, the authors did not analyze the possible effect of supplement on cancer response to therapy [21].

Surprisingly, in a multiethnic cohort study on 160 postmenopausal BC women and 289 controls, a positive association with statistical significance was found between circulating plasma CoQ10 levels and BC risk [24]. But this confusing discovery was later justified via the nonlinearity of the concentration-incidence correlation, after a second trial with opposite results, proposed by the same group of authors [2]. All these facts show a weak level of evidence for suggesting CoQ10 supplementation in BC setting.

Considering acceptable tolerability and safety profile of CoQ10 in the abovementioned studies and heterogeneity of the studies and consequent findings, implementation of well-designed studies with dose-optimization priorities would be mandatory for elucidation of the applicability of CoQ10 supplementation in the setting of breast neoplasms.

### Future perspective

In light of all the available facts containing considerable amount of positive preliminary evidence, demonstrating safety of CoQ10 products in BC populations and existing controversies, it
seems so encouraging to put effort into verification of the clinical effectiveness of this supplement as an adjunct, in different doses, as a mono-active-ingredient formulation, on histopathologic, constitutional and therapy-related complications of cancers of breast in the future.

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EXECUTIVE SUMMARY

- There is considerable amount of evidence that shows potential benefits of coenzyme Q10 (CoQ10) supplementation for breast cancer (BC) patients.
- Reported benefits of CoQ10 in BC field include potential preventive effects, increasing therapy effectiveness, amelioration of constitutional symptoms and controlling cancer therapy complications.
- There are controversial findings about the beneficial effects of CoQ10 in BC that require more studies for stratification in the future.

References
Papers of special note have been highlighted as:  • of interest;  •• of considerable interest
- Provides a good mechanistic foundation for potential usefulness of coenzyme Q10 on breast cancer.
3 Complementary treatments highlighted at recent meeting. Oncology (Williston Park, N.Y.) 13(2), 166 (1999).
- Report from the ANICA clinical study.
18 Yuvaraj S, Premkumar VG, Shanthi P, Vijayasarathy K, Gangadaran SG, Sachdanandam P. Effect of coenzyme Q(10), riboflavin and niacin on tamoxifen treated


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