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Mini Review

# Subjection between Breast Cancer and Body Mass Index, the Role of L-Carnitine in Prediction and Outcomes of the Disease

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## Abstract

Increasing the effectiveness of antitumor therapy in breast cancer patients who take L-carnitine during preoperative systemic antitumor therapy compared with patients receiving standard neoadjuvant systemic antitumor therapy served as a prerequisite for studying possible antitumor mechanisms of L-carnitine. The positive effect of L-carnitine is due to the transfer of palm-n-LC through the inner membrane into the mitochondrial matrix, which promotes the formation of a significant number of ATP molecules. It has also been shown that L-carnitine can have a double protective effect, enhancing the energy dynamics of the cell and inhibiting the hyperexcitability of the cell membrane, that making it an ideal nutrient for the prevention and treatment of cancer. This article summarizes the results of epidemiological and clinical studies of the use of L-carnitine in the treatment of breast cancer

**Keywords:** Body mass index (BMI); Breast cancer (BC); Obesity; Overall survival; L carnitine

## Introduction

The incidence of breast cancer in the world in general and in Ukraine in particular is growing. In 2017, in Ukraine the incidence reached 16 percent of female population, for which, the breast cancer ranked first in structure of oncological incidence among women. In analyzing the data of the National Cancer Registry of Ukraine, it should be noted, that in comparison with 2014 year, the prevalence rate of breast cancer in 2016has increased by 5,1%, that indicates importance of improvement diagnostic procedures and methods of treatment it [1]. Studying the scientific literature on this subject, we noticed that there is a strong biological relationship between obesity and a poor outcome of breast cancer. And having analysed the date of Ministry of Health in Ukraine it can be concluded, that about 26% of women in 2017 year had overweight or obesity.

Obesity has a chronic metabolic character, which is the result of the interaction of the endogenous factors, environmental conditions and lifestyle. Endogenous factors could be considered a violation of the genetic and hormonal balance. The external conditions and type of lifestyle include irregular rhythm nutrition, use of substandard products and sedentary lifestyle. Obesity is the first risk factor for metabolic syndrome, diabetes type II, cardiovascular disease and some forms of cancer, including breast cancer. Since overweight is a risk factor for breast cancer, there is reason to believe that among patients with breast cancer the percentage of obese women is higher than in the population. The risk of breast cancer in postmenopausal women by 30%, it is more than in premenopausal, women with obesity-50%. Furthermore it was proven that obesity is associated with poor prognosis in patients with breast cancer, regardless of menopausal status, and effectiveness of systemic medication breast cancer in patients that have over weight is lower than in patients with normal BMI.

Although obesity is associated with a poor outcome in women with breast cancer, it is unclear how weight loss after diagnosis will change its course and results. Recently, complementary and alternative medicine (CAM) is widely accepted among patients with breast cancer, which may provide several beneficial effects including reduction of therapy-associated toxicity, improvement of cancer-related symptoms, fostering of the immune system, and even direct anticancer effects [2]. L-carnitine is a metabolite of $C_4$ oil LC, which is involved in the transfer of palm-n-LC through the

inner membrane into the mitochondrial matrix and is a substrate for the formation of ATP molecules. Carnitine is a trim ethylated amino acid naturally synthesized in the liver, brain and kidneys from protein lysine and methionine. Several factors, such as sex hormones and glucagon, can influence the distribution and level of carnitine in tissues [3,4].

In the absence of L-carnitine, the inner membrane of the mitochondria becomes impermeable to fatty acids, which entails a chain of various metabolic disorders in the human body. Carnitine has a modulating effect on the function of acetylcholine excitatory neurotransmitter, glutamate excitatory amino acid, insulin growth factor-1 (IGF-1) and nitric oxide (NO)[3]. Also proved, that L-carnitine may have a dual protective effect by enhancing the energy dynamics of the cell and inhibiting cell membrane hyper excitability, which make it an ideal nutrient for cancer prevention and treatment [5]. In view of the foregoing, the study of the influence of the body mass index on the effectiveness of systemic treatment of breast cancer is an urgent scientific problem and a promising field of research. This article presents the information of epidemiological and clinical studies of the influence of the body mass index on the effectiveness of breast cancer treatment by individualizing therapeutic measures taking into account the characteristics of patient's metabolism.

**Studies on the Effects of BMI on The Course and Outcome of Breast Cancer and the Role of L-Carnitine in the Treatment of Cancer:** The effectiveness of the prescribing of L-carnitine for breast cancers' treatment, as well as the effect of BMI on the outcome of the disease is proven in epidemiological and clinical studies.

## Epidemiological and Clinical Studies

DSM Chan and co-authors [6] reported that women who have BMI> 30 course and outcomes of breast cancer are significantly worse than women with BMI <30. They proved, that women with BMI> 30 have the overall relative risk of total mortality 1.41, women with BMI of 25> 30 - 1.07. At the same time, for every 5 kg / $m^2$ of the increase BMI, the risk of both total mortality and mortality from breast cancer increased, namely by 18% and 14%, respectively M. Protani and co-authors [7] have shown that women with breast cancer, who are suffering in obesity, have lower survival rate than women with breast cancer without obesity. Recently published data of randomized clinical researches by ML Neuhouser and co-authors [8] demonstrated, that for women> 50 years old, with 2 and 3 stages of obesity (BMI> 35) is typically the development of GR+ breast cancer.

Similarly, B. Pajares et al. [9] who found significantly worse results for patients with BMI ≥35 compared with patients with BMI <25, stated that the magnitude of the effect depended on the cancer subtype (estrogen receptor (ER) / progesterone (PR) positive and HER2 negative, HER2 positive, triple negative). An analysis of the pooled data of the three adjuvant studies of the Eastern Cooperative Cancer Group showed significantly worse results for patients with obesity (BMI ≥ 30) than for patients with normal BMI with a hormonal receptor-positive disease. And it was noted absence of negative effect of obesity on survival in patients with other breast cancer subtypes. C Fontanella et al. [10] studied the effect of BMI on different molecular subtypes of breast cancer and concluded that in women with ER / PR-positive and HER2-negative breast cancer, as well as with TNBC, the risk of death is significantly higher than in other subtypes of cancer.

It is proved that even the highest BMI figures are not a risk factor for death for patients with luminal A-like subtype of breast cancer. The reason for this is that fatty tissue produces an excessive amount of estrogen, a high level of which is associated with an increased risk of developing breast, endometrial, ovarian and some other cancers. It has also been proven that the level of adipokine, that promotes cell proliferation, increases in the blood with increasing of level of fat in organism. And adiponectin, which people with obesity have less than people with normal BMI, can have anti proliferative effects. Such data can serve as evidence of the effect of BMI on the course and outcome of breast cancer. Yet another proof of influence developing metabolic syndrome on the course and outcome of breast cancer was proposed by R. Bhandari et al. [11]. They proved that that the presence of metabolic disorders (that is, the metabolic syndrome) is associated with an increased risk of breast cancer in adult women.

The above data led to the need to investigate medicines that contribute to fat burning, such as L-carnitine. Based on the data provided by Rania M. Khalil and co-authors [12], we can prove the positive effect of this medicine on the course and outcome of breast cancer. The study showed that patients who received Tamoxifen with L-carnitine had significant decrease of Her-2 / neu and IGF-1 level (P <0.05) in the serum compared with patients who received only Tamoxifen. Using of L-carnitine led to significant decrease Her-2 / neu level in the serum (P <0.05) compared to each of the control patients, namely, 59.5%. The effect of tamoxifen on IGF-1 (P <0.05) -decrease its level by 5.4% [13].However, it has been proved that using of L-carnitine in the treatment of ER+ breast cancer does not significantly reduce the level of estradiol, but leads to decrease both tumor markers CEA and CA15.3 (P <0.05,% decrease by 80.9% and 67, 8%, respectively) [13].

Using of L-carnitine in patients with breast cancer and obesity improves the metabolism of fatty acids in mitochondria, restores normal mitochondrial function and, thus, improves the general condition and quality of patients' life [14]. Carnitine may alsomimic some of the biological activities of glucocorticoids, particularly immunomodulation, via suppressing TNF-α and IL-12 release from monocytes (5). L-carnitine as adjuvant therapy in cisplatin-treated cancer patients proved a beneficial effect in reducing the cisplatin-induced organ toxicity [15]. It is possible that, the extremely lipophilic nature of carnitine may be responsible for the decrease in EGFbinding [16]. Carnitine may insert in the cell membrane

and/or interact with one of the many cellular enzymes having lipid substrates or cofactors. In addition, carnitine may interact directly with the EGFR [17].

Experimental evidence is available showing that ROS may induce the light and independent phosphorylation of the EGFR activating Her-2/neu. Moreover, the expression of the receptor is induced in conditions of oxidative stress [18]. L-carnitine, via its free radical scavenging and antioxidant properties, may inhibit ROS-mediated EGFR phosphorylation. It has been found that palmitoyl-carnitine can inhibit the activity of heart and brain protein kinase C in a competitive manner and subsequent phosphorylation of the EGFR [19]. Although the tumor markers and IGF-1 showed no significant difference in TAM-treated patients before and after administration of L-CAR, there was a tendency to decline after L-CAR supplementation [13]. The results of the above studies became a prerequisite for conducting clinical studies aimed at establishing the role of L-carnitine in the treatment of breast cancer.

To date, the search in the online clinical research registration system ClinicalTrials.gov using key words L-carnitine + breast cancer has revealed several studies evaluating the efficacy and safety of L-carnitine in the treatment of breast cancer patients. Analyzing the obtained results, we can conclude that L-carnitine was the drug of choice for neuropathies, as a consequence of chemotherapy, in patients with breast cancer.

## Conclusion

L-carnitine is widely used in clinical practice. However, recently this medicine causes growing interest among oncologists. In a number of studies, L-carnitine has proven itself as a medicine that capable, during the preoperative systemic antitumor therapy, to increase its effectiveness compared with standard neoadjuvant systemic antitumor therapy. And also, taking L-carnitine with neoadjuvant systemic antitumor therapy helps to increase the number of cases of complete morphological regression (V degree of therapeutic pathomorphosis). To date, there are several clinical studies that are researching using L-carnitine in various malignant tumors, the results of which are the basis for further in-depth study of the effect of the medicine in the treatment of malignant neoplasms.

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