

# Dyslipidemia and breast cancer

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## Δυσλιπιδαιμία και καρκίνος μαστού

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**Introduction:** Breast cancer is the most common cancer worldwide, accounting for 11.7% of all new cancer cases and has become the leading cause of cancer death in most countries. Modifiable and non-modifiable risk factors contribute to breast cancer development. Dyslipidemia as a modifiable factor is positively associated with breast cancer risk in postmenopausal women while it is also associated with poor prognosis in patients who with diagnosed disease.

The aim of the present study was to review the literature regarding the relationship between dyslipidemia and breast cancer.

**Methodology:** A literature search was conducted for scientific articles in the electronic databases Pub Med and Scopus, over the last 25 years. The following keywords were used for the search: dyslipidemia, breast cancer, women, as well as synonyms and combinations of the terms.

**Results:** According to literature, breast tissue proliferation (benign or malignant) is associated with changes in plasma lipid and lipoprotein levels. The concentration of certain apolipoproteins in plasma has been associated with breast cancer severity. Studies have demonstrated the important role of cholesterol, especially the metabolite 27-HC and its transporters in breast cancer development. Patients who have already developed breast cancer have higher plasma concentrations of LDL-cholesterol and very low density lipoprotein-cholesterol (VLDL). The LDL-cholesterol levels at diagnosis are predictive of tumor progression. In postmenopausal women, consumption of food with a high cholesterol content increases the risk of breast cancer development. Low-fat diet prolongs recurrence-free survival in women with estrogen receptor (ER)-negative breast cancer.

**Conclusions:** Given that dyslipidemia is a modifiable risk factor for the development and progression of breast cancer, educational interventions help individuals to adopt lifestyle changes that minimize breast cancer risk.

**Key-words:** Breast cancer, women, dyslipidemia,

## Introduction

Breast cancer is a common malignancy globally and the second leading cause of cancer death among women, despite improvements in diagnosis and advancements in treatment. According to estimates in the United States, one in eight women or 13%, will be diagnosed with invasive breast cancer, and one in 43 or 2%, will die from the disease. In 2024, the new cases of invasive breast cancer were approximately 310.720 among women in USA.<sup>1</sup>

Interestingly, breast cancer incidence is steadily increasing, which is mainly attributed to the ageing population in Europe. Several modifiable factors (dietary, alcohol, smoking, physical inactivity, obesity) and non-modifiable factors (female gender, age and heredity) are to be held responsible for high breast cancer incidence.<sup>2</sup> Compared to healthy individuals, the incidence of dyslipidemia is higher among breast cancer patients. Dyslipidemia is a risk factor for poor breast cancer prognosis. Chemotherapy after breast operation implies a long-term deterioration of dyslipidemia.<sup>3</sup>

As dyslipidemia is defined the disorder including elevated plasma triglycerides (TG), elevated total cholesterol (TC), high levels of low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL). Low-density lipoprotein cholesterol (LDL-C) is a risk factor for cardiovascular diseases. In breast cancer patients, cardiovascular deaths account for 16.3% of all deaths.<sup>4</sup>

One of the first observations linking cholesterol and cancer was made in 1909.<sup>5</sup> Presently, more than 100 years later, the relationship between cholesterol and increased cancer risk remains unclear. The issue is addressed in literature, with controversial results. More in detail, some studies indicate cholesterol as a significant risk factor for breast cancer whereas other suggest a protective effect.<sup>6,7,8</sup>

The **purpose** of this review was to explore the association between breast cancer and dyslipidemia.

## Methodology

A literature search was conducted for scientific articles in the electronic databases Medline (PubMed) and Scopus, over the last 25 years. The following keywords were used during the search: dyslipidemia, breast cancer, women, as well as synonyms and combinations of the terms. The criteria for including an article in the study were: a) publication language in English, b) relevancy to subject under study and c) publication in a valid scientific journal.

## Review of Literature

Dyslipidemia leads to increased cholesterol content in cell membranes, affecting membrane fluidity and subsequent signaling. In addition, the metabolite 27-hydroxycholesterol (27HC) may act as an estrogen, increasing the proliferation of estrogen receptor (ER)-positive breast cancer cells.<sup>5</sup>

A noticeable result from a recent study is higher LDL-cholesterol and very-low density lipoprotein cholesterol (VLDL) in patients with breast cancer, although no association between HDL or total cholesterol and breast cancer was evident.<sup>9</sup> Other relevant study demonstrated that when adjusted for obesity, the dietary cholesterol intake was strongly associated with increased risk of breast cancer in postmenopausal but not in premenopausal women.<sup>10</sup> These observations have been confirmed by other epidemiological studies and a large prospective study suggesting an association between dietary cholesterol consumption and breast cancer risk.<sup>11,12</sup> It is worth noting that elevated cholesterol has also been associated with other cancers, such as prostate cancer.<sup>5,13</sup>

The relationship between circulating cholesterol carried by low-density lipoproteins (LDL) or high-density lipoproteins (HDL) and breast cancer is matter of controversy. However, in literature is cited a positive association between LDL and breast cancer, while HDL is rather negatively associated with the disease.<sup>14</sup> Apolipoproteins play essential role in maintaining the structural integrity and functional specificity of plasma lipoproteins. They are directly involved in various metabolic processes of lipoproteins, including secretion, prevention of premature removal from the circulation, binding to cell surface receptors and activation of lipolytic enzymes.<sup>14,15</sup>

In addition to their role in lipoprotein metabolism, apolipoproteins are shown to be involved in breast cancer development. The plasma level of some apolipoproteins has been associated with the severity of breast cancer. For example, low plasma apoA-I levels appeared to independently predict poor clinical outcome in patients with invasive ductal breast cancer.<sup>16</sup> In another study, lower concentrations of apoC-I and apoC-II were found in breast cancer patients compared with controls, while the concentration of apoC-III was higher.<sup>17</sup> The concentration of apoE in plasma was positively associated with breast cancer malignancy.<sup>18</sup> Higher plasma concentrations of apoD are observed in women with advanced breast cancer.<sup>14</sup> It is known that Apolipoprotein E exists in plasma in a polymorphic form. The main isoforms are

apoE2, apoE3 and apoE4, which lead to six phenotypes, depending on the inherited E alleles. Studies suggest an association between the presence of the E4 allele and breast cancer.<sup>14,19</sup>

Furthermore, cancer cells exhibit specific alterations in various aspects of lipid metabolism, which affect the availability of structural lipids for membrane synthesis, the contribution of lipids to energy homeostasis, and lipid signaling functions, including the activation of pathways associated with inflammation. All of these changes are associated with cellular processes, including cell growth, proliferation, differentiation, and motility.<sup>20,21</sup>

The interplay between cholesterol, lipoproteins, proinflammatory signaling pathways, and tumor growth has been studied primarily in breast cancer cells and in vivo experimental models. Furthermore, in humans, both benign and malignant breast tissue proliferation were associated with changes in plasma lipid and lipoprotein levels, although epidemiological data regarding relationship between lipoproteins and breast cancer showed inconclusive results.<sup>21-24</sup>

Since cholesterol is mainly transported by LDL and HDL, several clinical trials have linked it to breast cancer. A clinical study in which the lipid profile was assessed in women with breast cancer showed that LDL cholesterol (LDL-C) levels at diagnosis were predictive of breast tumor progression. A systemic LDL-C level above 117 mg dL<sup>-1</sup> was found to be a predictor of tumor stage and was positively associated with a worse prognosis due to higher histological grade, higher proliferation rate, and more advanced clinical stage.<sup>25</sup> In addition, patients with LDL-C above 144 mg dL<sup>-1</sup> were prone to develop lymph node metastases.<sup>25</sup> More importantly, genetically elevated LDL-C is associated with a higher risk of breast cancer.<sup>24</sup> However, other meta-analyses and prospective studies found no association between LDL-C and breast cancer risk.<sup>22,23,26,27</sup> Relevant studies illustrated that LDL-C or non-HDL were inversely associated with breast cancer risk.<sup>28,29</sup>

Regarding HDL-C, there has also been discordance in the results. A prospective study with a follow-up of 11.5 years found an inverse association between HDL-C and breast cancer risk,<sup>30</sup> while retrospective clinical data showed that reduced HDL-C levels were significantly associated with worse overall survival in breast cancer patients.<sup>31</sup> In contrast, a study showed that high HDL-C increases the risk of estrogen receptor (ER)-positive breast cancer.<sup>24</sup> However, other recent study showed no association between serum lipid and breast cancer risk

or survival.<sup>32</sup> Although some studies have failed to find associations between lipoproteins and breast cancer, the results of other large clinical trials show a direct relationship between LDL-C and breast cancer risk, as well as an inverse relationship between HDL-C and breast cancer risk.<sup>20</sup>

The Women's Nutritional Management Study (WINS) illustrated that a low-fat diet extended recurrence-free survival in women with Estrogen receptor (ER)-negative breast cancer.<sup>33</sup> The fact that ER-negative breast cancer cells receive and store cholesterol to different degrees may partially explain the variable effect of a low-fat diet on breast cancer recurrence in humans.<sup>34</sup> Another study found that LDL-C induced proliferation in ER-positive breast cancer cells BT-474.<sup>35</sup> This discrepancy is explained by the fact that BT-474 cells typically express the Her2 (ErbB2) receptor. Furthermore, high plasma LDL-C levels is found to be associated with Her2-positive breast cells.<sup>25</sup> Notably, Her2-positive and triple-negative subtypes are aggressive breast cancers.<sup>36</sup>

Lipid peroxidation is associated with carcinogenesis. Lipid peroxidation metabolites cause structural changes in DNA and reduce the capacity for DNA repair through their direct interaction with repair enzymes. LDL oxidation affects both protein and lipid content, resulting in the formation of peroxidation metabolites. Breast cancer patients have increased serum levels of oxidized LDL (oxLDL). Furthermore, serum oxLDL levels have been associated with an increased risk of breast cancer.<sup>37</sup> Oxidized LDL is reported to induce pro-oncogenic signaling in MCF10A cells. Specifically, cells treated with oxLDL showed a dose-dependent stimulation of proliferation mediated by stimulation of the microRNA miR-21, which, in turn, activated the relevant pro-inflammatory PI3K/Akt signaling pathways.<sup>38</sup>

Controversy exists over the relationship between HDL-C levels and breast cancer risk. In vitro assays have shown that HDL stimulates proliferation in both ER-positive and ER-negative breast cancer cell lines in a dose-dependent manner, but ER-negative cells showed a higher response.<sup>20</sup>

Apolipoprotein A-I promotes cholesterol release from cells, possesses anti-inflammatory, antioxidant, and anti-apoptotic properties, and influences innate immune system.<sup>39</sup> ApoA-I levels are consistently inversely associated with breast cancer risk.<sup>40</sup> Especially, for high-density lipoprotein (HDL) which is the predominant lipoprotein cholesterol that transports cholesterol to the major steroidogenic organs, it is safe to say that its anticancer

activity is attributable to its pleiotropic properties, including its antioxidant activity, regulation of cytokine production, inhibition of apoptosis, and promotion of cell growth and migration.<sup>41-45</sup> Possibly, HDL antagonizes the two main features of cancer progression through its potent antioxidant and anti-inflammatory effects.<sup>46,47</sup>

A recent study by Koukoularis et al.,<sup>2</sup> among 501 women with breast cancer demonstrated that 50.3% had high total cholesterol levels (240+ mg/dl), 33.5% had high LDL levels (160+ mg/dl) and 38.5% had high TG levels (200+mg/dl). Women with non-invasive non-ductal carcinoma had higher plasma concentrations of total cholesterol, TG, and lower HDL.<sup>2</sup> Women with total cholesterol levels above 240 mg/dL were at higher risk of developing breast cancer than women with cholesterol levels below 160 mg/dL.<sup>12</sup>

Dyslipidemia is often encountered in clinical practice, threatening patients' overall health. Given the asymptomatic nature of dyslipidemia, early recognition by health professionals and provision of elaborate and accurate information is an important caring aspect. Indeed, information should be an integral component in providing high-quality care to patients with dyslipidemia or even when screening new cases.<sup>48</sup> Interestingly, patients with low level of knowledge fail to seek for up-to-date information about the disease and its

treatment.<sup>49</sup> Strikingly more, individuals with hyperlipidemia are at high risk of anxiety and depression. The relationship between hyperlipidemia and depression is bi-directional.<sup>50</sup> Emotional burden (anxiety, depression) is related with poor self-care behavior, and as a general rule, it predicts poor adherence to treatment recommendations.<sup>50,51</sup> Therefore, eliminating this emotional disturbance in patients with dyslipidemia may be a cost effective strategy to minimize the related breast cancer risk.

### Conclusions

Results suggest a direct association for LDL-C and an inverse relationship for HDL-C and breast cancer risk. However, these findings have not been replicated in all epidemiological studies and are still under debate. Research studies have established the important role of cholesterol, especially the metabolite 27-HC, and its transporters in the development of breast cancer. Both LDL and HDL, and their modified forms (oxLDL) may promote breast cancer through various mechanisms.

The observed clinical or methodological differences in study design, including variation in geographic regions, menopause, duration of follow-up, may explain the discrepancies in association between breast cancer and dyslipidemia.

## ΠΕΡΙΛΗΨΗ

### Δυσλιπιδαιμία και καρκίνος μαστού

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**Εισαγωγή:** Ο καρκίνος μαστού είναι ο πλέον συχνός καρκίνος παγκοσμίως, αντιπροσωπεύοντας το 11,7% όλων των νέων περιπτώσεων καρκίνου και έχει εξελιχθεί στην κύρια αιτία θανάτου από καρκίνο στις περισσότερες χώρες. Τροποποιησιμοι και μη τροποποιησιμοι παράγοντες κινδύνου ευθύνονται για την εκδήλωση καρκίνου μαστού. Η δυσλιπιδαιμία ως τροποποιησιμος παράγοντας συνδέεται θετικά με τον κίνδυνο καρκίνου μαστού σε μετεμμηνοπαυσιακές γυναίκες ενώ σχετίζεται επίσης με φτωχή πρόγνωση σε ασθενείς με διαγνωσμένη νόσο. **Σκοπός** της παρούσας μελέτης ήταν η ανασκόπηση της βιβλιογραφίας αναφορικά με τη σχέση μεταξύ δυσλιπιδαιμίας και καρκίνου μαστού. **Μεθοδολογία:** Διεξήχθη βιβλιογραφική αναζήτηση για επιστημονικά άρθρα στις ηλεκτρονικές βάσεις δεδομένων Pub Med και Scopus, τα τελευταία 25 χρόνια. Για την αναζήτηση χρησιμοποιήθηκαν οι ακόλουθες λέξεις-κλειδιά: δυσλιπιδαιμία, καρκίνος του μαστού, γυναίκες, καθώς και συνώνυμα και συνδυασμοί των όρων. **Αποτελέσματα:** Σύμφωνα με τη βιβλιογραφία, ο πολλαπλασιασμός του ιστού του μαστού (καλοήθης ή κακοήθης) συσχετίζεται με αλλαγές στα επίπεδα λιπιδίων και λιποπρωτεϊνών στο πλάσμα. Η συγκέντρωση ορισμένων απολιποπρωτεϊνών στο πλάσμα έχει

συσχετιστεί με τη σοβαρότητα του καρκίνου μαστού. Μελέτες κατέδειξαν τον σημαντικό ρόλο της χοληστερόλης, ιδιαίτερα του μεταβολίτη 27-HC και των μεταφορέων του στην ανάπτυξη καρκίνου μαστού. Οι ασθενείς που έχουν ήδη εκδηλώσει καρκίνο μαστού έχουν υψηλότερες συγκεντρώσεις στο πλάσμα LDL-χοληστερόλης και πολύ χαμηλής πυκνότητας λιποπρωτεΐνης-χοληστερόλης (VLDL). Τα επίπεδα της LDL χοληστερόλης κατά τη διάγνωση είναι προγνωστικά της εξέλιξης του όγκου. Στις γυναίκες μετά την εμμηνόπαυση, η κατανάλωση τροφής υψηλής περιεκτικότητας σε χοληστερόλη αυξάνει τον κίνδυνο εκδήλωσης καρκίνου μαστού. Η διατροφή χαμηλής περιεκτικότητας σε λιπαρά παρατείνει την επιβίωση χωρίς υποτροπές σε γυναίκες με καρκίνο μαστού αρνητικό στους υποδοχείς οιστρογόνων (ER). **Συμπεράσματα:** Δεδομένου ότι η δυσλιπιδαιμία είναι τροποποιήσιμος παράγοντας κινδύνου για την ανάπτυξη και εξέλιξη του καρκίνου μαστού, οι εκπαιδευτικές παρεμβάσεις βοηθούν τα άτομα να υιοθετήσουν αλλαγές στον τρόπο ζωής που ελαχιστοποιούν τον κίνδυνο καρκίνου μαστού.

**Λέξεις-κλειδιά:** Καρκίνος μαστού, γυναίκες, δυσλιπιδαιμία

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