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*Review*

# Lipid Profiles in Breast Cancer: Clinical Associations and Biological Insights

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## Abstract

Alterations in lipid metabolism are increasingly recognized as important contributors to breast cancer biology. Lipids regulate membrane structure, intracellular signaling, and energy homeostasis, and cancer cells undergo lipid metabolic reprogramming to support tumor growth and progression. This narrative review summarizes current evidence on the relationship between circulating lipid profiles and breast cancer risk, tumor characteristics, and outcomes, with a focus on total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), as well as the effects of endocrine therapies on lipid metabolism. Epidemiological studies show heterogeneous and lipid-specific associations that vary by menopausal status, tumor subtype, and study design. Triglycerides and LDL-C are most consistently linked to aggressive tumor features and disease progression, whereas total cholesterol appears to reflect broader metabolic and hormonal disturbances rather than a direct causal role. HDL-C shows inconsistent associations, likely due to functional heterogeneity not captured by circulating HDL-C levels alone. Mechanistic studies support a role for lipid metabolism in promoting tumor growth, invasion, angiogenesis, and therapy resistance. Endocrine therapies further modify lipid profiles, with tamoxifen generally reducing total cholesterol and LDL-C while increasing triglycerides, and aromatase inhibitors showing largely neutral effects in recent population-based studies. Overall,

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circulating lipid fractions are not suitable as standalone biomarkers but may provide clinically relevant information when interpreted in the context of tumor biology, metabolic health, and long-term survivorship care.

**Keywords:** Breast cancer, circulating lipids, dyslipidemia, LDL cholesterol, HDL cholesterol, triglycerides, review.

## Introduction

Breast cancer remains a leading cause of cancer-related morbidity and mortality among women worldwide (1). Although established risk factors such as age, reproductive history, genetic susceptibility, and hormonal exposure are well defined, growing evidence suggests that metabolic disturbances also contribute to breast cancer development. Obesity, insulin resistance, and dyslipidemia – often coexisting within metabolic syndrome – have attracted increasing interest due to their potential roles in endocrine dysregulation, chronic inflammation, and altered energy metabolism (2).

Lipids are fundamental components of cellular structure and function (3). Beyond serving as energy substrates, they influence membrane dynamics, intracellular signaling, redox balance, and immune responses. Cancer cells display alterations in lipid uptake, synthesis, storage, and oxidation, collectively referred to as lipid metabolic reprogramming (4). In breast cancer, both systemic lipid abnormalities and tumor-related changes have been reported, suggesting a dynamic interaction between host metabolism and tumor biology (5).

Despite extensive investigation, the clinical and biological significance of circulating lipid profiles in breast cancer remains incompletely understood. Reported associations vary widely across studies, likely reflecting differences in study design, menopausal status, tumor subtype, ethnicity, and analytical methodology. This review critically examines the current evidence linking circulating lipid fractions to breast cancer risk, tumor characteristics, and disease outcomes, with particular emphasis on lipid-specific patterns and underlying biological mechanisms.

## Methods

This article is a narrative review of the published literature examining the association between circulating lipid profiles and breast cancer risk, tumor characteristics, prognosis, and the effects of endocrine therapies on lipid metabolism. A non-systematic literature search was performed using the electronic databases PubMed and Scopus, as well as Google Scholar. Relevant articles were identified using combinations of keywords related to breast cancer, lipid metabolism, dyslipidemia, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, tamoxifen, and aromatase inhibitors. Priority was given to peer-reviewed articles published in English, with emphasis on epidemiological studies, meta-analyses, mechanistic research, and clinically relevant original studies, primarily from the last decade. The selection of literature was based on relevance to the scope of the review and contribution to the understanding of lipid-specific associations and underlying biological mechanisms. No formal systematic review protocol or predefined inclusion and exclusion criteria were applied.

## Overview of Lipid Metabolism and Dyslipidemia

Circulating lipids are commonly assessed through measurements of total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). LDL particles are the primary carriers of cholesterol to peripheral tissues, whereas HDL particles mediate reverse cholesterol transport to the liver. Triglycerides, transported mainly in very-low-density lipoproteins (VLDL) and chylomicrons, represent a major energy reservoir.

Dyslipidemia is characterized by elevated TG, TC, and LDL-C levels and/or reduced HDL-C levels. It frequently accompanies obesity, insulin resistance, and chronic low-grade inflammation – conditions increasingly recognized as contributors to cancer development. Importantly, lipid metabolism is tightly regulated by sex hormones, particularly estrogens, providing a strong biological rationale for interactions between lipid homeostasis and breast cancer pathophysiology.

## Circulating Lipid Profiles and Breast Cancer Risk

Although lipid fractions share metabolic interdependence, they appear to exhibit distinct and sometimes opposing relationships with breast cancer risk and progression. The available evidence suggests considerable heterogeneity in both the direction and magnitude of associations across lipid parameters. Each major lipid fraction is therefore considered separately.

### Total Cholesterol

TC is among the most frequently examined lipid parameters in breast cancer research. Several case–control studies, including the Bangladeshi cohort reported by Chowdhury *et al*., have demonstrated higher TC levels in women with breast cancer compared with those with benign breast disease or healthy controls, even after adjustment for potential confounders (6). A large Korean prospective study examining multiple cancer types also reported an association between TC levels and breast cancer risk (7).

However, findings from large-scale epidemiological studies remain inconsistent. As summarized by Cedó *et al.,* several cohort studies and Mendelian randomization analyses fail to support a clear causal relationship between TC and breast cancer incidence (8). These discrepancies suggest that TC may primarily reflect underlying metabolic or hormonal disturbances rather than acting as a direct driver of tumor initiation. Supporting this interpretation, studies in other malignancies demonstrate that dynamic changes in cholesterol may be more clinically informative than single measurements. In gastric cancer, postoperative increases in total cholesterol have been associated with significantly poorer overall and recurrence-free survival, independent of tumor stage (9). Notably, these increases were observed despite weight loss and were linked to preoperative hypoalbuminemia, suggesting that elevated cholesterol reflects metabolic dysregulation rather than improved nutritional status. Biological relevance is more likely mediated through downstream cholesterol metabolites, particularly 27-hydroxycholesterol, which has been implicated in estrogen receptor–positive disease. Clinically, TC should therefore be interpreted as a non-specific metabolic marker, best evaluated in conjunction with other lipid fractions and patient- or tumor-specific characteristics.

### Triglycerides

Among circulating lipid fractions, TGs have shown relatively consistent associations with breast cancer in observational studies, although effect sizes vary by menopausal status and study design. In a systematic review and meta-analysis focused on premenopausal women, Wu *et al*. reported significantly higher TG levels in patients with breast cancer compared with controls, whereas TC and HDL-C did not differ significantly (10). Similar findings have been reported in individual case–control studies comparing malignant, benign, and healthy populations (6).

Evidence from genetic epidemiology suggests a different perspective on the role of triglycerides in breast cancer initiation. Using a two-sample Mendelian randomization approach, Zhang *et al.* identified an inverse association between genetically predicted TG levels and overall breast cancer risk, including luminal A and HER2-enriched subtypes (11). These findings indicate that lifelong genetically determined TG levels may not increase susceptibility to breast cancer. Notably, the same study reported a positive association between elevated TG levels and poorer survival in estrogen receptor–negative breast cancer, suggesting context-dependent effects related to tumor subtype and disease stage.

Mechanistic studies provide biological plausibility for a role of TGs in disease progression rather than initiation. TGs are transported predominantly in VLDL particles, which increase fatty acid availability to peripheral tissues. Experimental evidence demonstrates that TG-rich lipoproteins promote epithelial–mesenchymal transition, angiogenesis, and invasive behavior in breast cancer cells through activation of PI3K/AKT signaling pathways (5). Adipocyte-driven mechanisms further contribute to a tumor-supportive microenvironment characterized by inflammation and metabolic fueling (12).

Additional insight is provided by studies evaluating the triglyceride–glucose (TyG) index, a composite marker of insulin resistance. A recent systematic review and meta-analysis reported that higher TyG index values were associated with breast cancer in case–control and cross-sectional studies and demonstrated moderate diagnostic accuracy in distinguishing malignant from benign breast lesions (13). However, cohort studies did not confirm a strong association with new cases of breast cancer, reinforcing the notion that TG-related metabolic disturbances are more closely linked to tumor presence and progression than to cancer initiation.

## Low-density Lipoprotein Cholesterol

LDL-C emerges as the lipid fraction with the most coherent convergence between epidemiological associations and mechanistic evidence. In a meta-analysis restricted to premenopausal women, significantly higher LDL-C levels were observed in patients with breast cancer compared with controls, with larger effect sizes than those reported for TGs, while no significant differences were detected for TC or HDL-C (10).

Clinical studies further suggest that LDL-C levels at diagnosis correlate with adverse tumor characteristics. Elevated LDL-C concentrations have been associated with higher tumor grade, increased proliferative index, more advanced clinical stage, and a greater likelihood of lymph node involvement (8, 14). Although associations with disease incidence are less consistent, these recurrent links to tumor aggressiveness indicate that LDL-C may be particularly relevant to disease behavior.

Strong biological plausibility underpins these observations. LDL particles are the principal vehicles for cholesterol delivery to peripheral tissues and are actively internalized by breast cancer cells *via* LDL receptor–mediated uptake. Experimental studies demonstrate that LDL and VLDL – but not HDL – promote breast cancer cell proliferation, migration, invasion, epithelial–mesenchymal transition, and angiogenesis through activation of PI3K/AKT signaling pathways (5). *In vivo,* VLDL exposure promoted lung metastasis, reinforcing the role of LDL-related lipoproteins in metastatic progression.

Beyond cholesterol transport, LDL-C influences membrane composition and signaling platforms. Cholesterol-enriched lipid rafts facilitate the spatial organization of growth factor receptors and oncogenic signaling cascades, including epidermal growth factor receptor and estrogen receptor pathways (15). Experimental studies further demonstrate that cholesterol accumulation enhances activation of key survival pathways, including PI3K/Akt and mTOR signaling, through stabilization of lipid raft domains (16). These pathways are central to cancer cell proliferation and survival, highlighting the functional importance of cholesterol-rich membrane structures in tumor progression.

In estrogen receptor–positive disease, cholesterol metabolism is further linked to tumor growth through the generation of 27-hydroxycholesterol, an endogenous selective estrogen receptor modulator capable of promoting proliferation and metastasis (8).

Recent studies reinforce the relevance of LDL-related lipid metabolism in breast cancer progression. Gene signatures enriched for cholesterol and fatty acid pathways have been associated with poor prognosis, altered immune infiltration, and therapy response, particularly in estrogen receptor–positive tumors (17). Collectively, these findings position LDL-C as a marker of tumor-supportive metabolic environments, with particular relevance to disease progression rather than initiation.

## High-density Lipoprotein Cholesterol

HDL-C has traditionally been regarded as protective in cardiovascular disease. However, its role in breast cancer appears substantially more complex and less consistent than that of other lipid fractions. Epidemiological studies have reported inverse, null, or positive associations between HDL-C levels and breast cancer risk, depending on population characteristics, menopausal status, and tumor subtype. In a meta-analysis focused on premenopausal women, HDL-C levels did not differ significantly between patients with breast cancer and controls (10).

Genetic studies further complicate interpretation, suggesting that genetically determined HDL-C levels may be associated with increased risk of estrogen receptor–positive breast cancer (8). These findings underscore an important limitation of using circulating HDL-C concentration as a surrogate for HDL biological activity and highlight the need to consider HDL functionality rather than quantity alone.

Mechanistic studies highlight the functional heterogeneity of HDL particles. Under physiological conditions, HDL exerts anti-inflammatory, antioxidant, and immune-modulatory effects. However, chronic inflammation, oxidative stress, and metabolic dysfunction can impair these protective properties. Oxidized or glycated HDL may lose anti-inflammatory capacity and potentially acquire pro-tumorigenic effects (8, 15).

HDL also participates indirectly in hormone-related signaling through the transport and metabolism of cholesterol derivatives such as 27-hydroxycholesterol, linking HDL metabolism to estrogen receptor–positive tumor biology (8). Emerging evidence further suggests interactions between HDL metabolism and the immune microenvironment, including effects on macrophage polarization and immune cell cholesterol homeostasis (15). Together, these findings indicate that HDL functionality, rather than circulating HDL-C levels, is likely to be the critical determinant of its role in breast cancer.

## Impact of Tamoxifen and Aromatase Inhibitors on Lipid Profiles

Breast cancer treatment, especially endocrine therapy, is known to affect lipid metabolism. Tamoxifen, a selective estrogen receptor modulator used in hormone receptor–positive breast cancer, has been shown to improve several lipid parameters. Studies consistently report a reduction in TC and LDL-C during tamoxifen therapy. These effects are thought to be related to the estrogen-like action of tamoxifen on the liver (18). At the same time, tamoxifen treatment is associated with an increase in TG levels, which has been observed in both short- and mid-term follow-up studies (19). The effect of tamoxifen on HDL-C is less consistent, with studies reporting an increase, no change, or a slight decrease (19).

Aromatase inhibitors, which strongly reduce estrogen production, show more variable effects on lipid profiles compared with tamoxifen. Earlier clinical studies suggested that some aromatase inhibitors, particularly anastrozole and letrozole, may increase TC and LDL-C, while exemestane appeared to have neutral or mildly favorable effects on lipids (20). However, more recent large-scale real-world data do not support a major negative effect of aromatase inhibitor therapy on lipid levels. A nationwide Danish cohort study of postmenopausal women with early breast cancer found no clinically relevant differences in changes in LDL cholesterol, HDL-C, TC, or TGs between women treated with aromatase inhibitors and those not receiving endocrine therapy (21). These findings suggest that although endocrine therapies can alter lipid metabolism, their overall impact on lipid-related cardiovascular risk may be limited, but regular lipid monitoring remains important in long-term breast cancer survivors.

Beyond systemic lipid changes, cholesterol metabolism may directly influence endocrine therapy response. Experimental evidence shows that cholesterol accumulation contributes to acquired resistance to tamoxifen by activating alternative proliferative pathways such as PI3K/Akt and MAPK signaling (16). Conversely, depletion of intracellular cholesterol enhances tamoxifen-induced apoptosis and restores drug sensitivity in resistant breast cancer cells.

## Discussion

The present review highlights that the relationship between circulating lipid fractions and breast cancer is multifaceted and lipid-specific, reflecting the complex interplay between systemic metabolism, tumor biology, hormonal signaling, and disease stage (Table I). Rather than supporting a uniform role for dyslipidemia, the available evidence indicates that individual lipid fractions differ substantially in their biological relevance and clinical implications (8).

A recurring theme across the literature is the divergence between observational associations and causal inference, particularly evident for TGs and TC. Case–control and cross-sectional studies frequently report elevated levels of these lipids in women with breast cancer, especially in premenopausal populations (6, 10). In contrast, genetic studies and prospective cohorts often fail to confirm a direct causal role in cancer initiation (11). This discrepancy underscores the importance of temporality and metabolic context. Lipid profiles measured at or near diagnosis likely reflect metabolic disturbances associated with obesity, insulin resistance, inflammation, and tumor–host interactions, rather than pre-existing etiological exposures. Consequently, circulating lipids should be interpreted primarily as indicators of tumor-supportive metabolic environments rather than independent carcinogenic factors. Evidence from other cancer types reinforces this concept. In gastric cancer, increases in serum cholesterol following surgery have been associated with early recurrence and poor survival outcomes, independent of traditional prognostic factors (9). Importantly, these changes were linked to markers of poor nutritional and metabolic status, indicating that elevated cholesterol may reflect tumor-promoting systemic conditions rather than a beneficial physiological state.

Among the lipid fractions examined, LDL-C emerges as the most biologically coherent marker in breast cancer. Clinical studies consistently associate elevated LDL-C levels with aggressive tumor characteristics, including higher grade, nodal involvement, and advanced stage (8). These observations are strongly supported by mechanistic evidence demonstrating that LDL and related lipoproteins directly promote breast cancer cell proliferation, epithelial–mesenchymal transition, invasion, angiogenesis, and metastatic dissemination through activation of PI3K/AKT signaling pathways (5). In hormone receptor–positive disease, LDL-mediated cholesterol delivery further integrates with estrogen signaling *via* the generation of 27-hydroxycholesterol, an endogenous selective estrogen receptor modulator implicated in tumor growth and metastasis (8). Together, these findings position LDL-C at the intersection of systemic metabolism, oncogenic signaling, and hormonal regulation, suggesting a particular relevance to disease progression rather than initiation. This mechanistic link extends to treatment resistance, where cholesterol accumulation has been shown to promote endocrine therapy resistance through activation of PI3K/Akt/mTOR signaling pathways and stabilization of lipid raft–dependent signaling (16). Importantly, targeting cholesterol metabolism in experimental models enhances apoptosis and restores sensitivity to tamoxifen, suggesting that lipid metabolic pathways may represent actionable therapeutic targets.

TGs display a different, but equally informative, pattern. Observational and meta-analytic studies consistently demonstrate higher TG levels in patients with breast cancer, particularly among premenopausal women (10), whereas genetic evidence argues against a causal role in disease onset (11). This apparent contradiction is best explained by the biological meaning of TGs in clinical settings. Elevated TG levels reflect insulin resistance, hepatic VLDL overproduction, and adipocyte dysfunction

Table I. *Circulating lipid fractions and their associations with breast cancer.*

| Lipid fraction | Breast cancer risk | Tumor characteristics/ outcomes | Mechanistic evidence | Effect of endocrine therapy |
|---|---|---|---|---|
| Total cholesterol (TC) (1-6) | Higher TC reported in several case–control and population studies, but no consistent causal association in cohort or Mendelian randomization analyses | No consistent association with aggressiveness or prognosis | Biological effects likely mediated through cholesterol metabolites (*e.g.*, 27-hydroxycholesterol) rather than TC itself | ↓ TC with tamoxifen; largely neutral effects with aromatase inhibitors |
| Triglycerides (TG) (1, 7-12) | Frequently elevated in breast cancer patients, particularly in premenopausal women; genetically predicted TG inversely associated with overall risk | Associated with aggressive tumor features and poorer survival, especially in ER-negative disease | TG-rich lipoproteins (VLDL) promote proliferation, invasion, angiogenesis, EMT, and PI3K/AKT activation; reflect insulin resistance and adipocyte dysfunction | ↑ TG with tamoxifen; generally neutral effects with aromatase inhibitors |
| Low-density lipoprotein cholesterol (LDL-C) (3, 4, 6-8, 13, 14) | Modest association with risk, particularly in premenopausal women | Consistently associated with higher grade, nodal involvement, advanced stage, and tumor progression | LDL receptor–mediated uptake promotes proliferation, invasion, EMT, angiogenesis; cholesterol-rich lipid rafts; 27-hydroxycholesterol–ER signaling | ↓ LDL-C with tamoxifen; neutral effects with aromatase inhibitors in recent population studies |
| High-density lipoprotein cholesterol (HDL-C) (3, 4, 6, 8, 12, 14) | Inconsistent associations (inverse, null, or positive); genetic evidence suggests possible increased risk in ER+ disease | No consistent association with prognosis | Functional heterogeneity of HDL; inflammation-induced dysfunction; altered immune modulation; involvement in cholesterol metabolite transport | Variable effects with tamoxifen; largely neutral with aromatase inhibitors |
| Composite indices (*e.g.*, TyG index) (9, 11) | Associated with breast cancer in case–control and cross-sectional studies; limited evidence for incident risk | Moderate diagnostic accuracy for distinguishing malignant from benign breast lesions | Reflects insulin resistance, hepatic VLDL overproduction, metabolic inflammation | Indirectly influenced by endocrine therapy through metabolic changes |

– metabolic states that increase lipid availability and promote chronic inflammation. Experimental studies show that TG-rich lipoproteins actively support invasive and angiogenic phenotypes (5), providing a mechanistic basis for the association between hypertriglyceridemia and poorer outcomes, especially in estrogen receptor–negative breast cancer (11). TGs therefore appear to function as markers and mediators of tumor progression rather than initiators of carcinogenesis.

In contrast, TC shows limited specificity in breast cancer. Although elevated levels are frequently observed in case–control studies, inconsistent findings across cohorts and genetic analyses suggest that TC primarily reflects broader metabolic and hormonal disturbances rather than exerting direct tumor-promoting effects (8). Its biological relevance appears largely mediated through downstream pathways involving lipoprotein distribution and cholesterol metabolites, rather than through total circulating levels *per se*.

HDL-C presents the greatest interpretative challenge. Epidemiological associations with breast cancer risk and outcomes are highly inconsistent, and genetic studies suggest possible subtype-specific effects (8). Mechanistic evidence indicates that HDL functionality, rather than HDL-C concentration, is likely to be the critical determinant of its role in cancer biology. Inflammatory remodeling, oxidation, or glycation of HDL particles can impair their anti-inflammatory and antioxidant properties, potentially shifting HDL toward neutral or even detrimental effects (8). Moreover, HDL participates in the transport and metabolism of cholesterol derivatives such as 27-hydroxycholesterol, indirectly linking HDL metabolism to estrogen receptor signaling (8). These considerations highlight the limitations of relying on HDL-C concentration alone in breast cancer research.

An additional layer of complexity arises from the tumor microenvironment, where adipocytes, immune cells, and stromal components interact dynamically with lipid metabolism. Adipocyte-derived fatty acids and TGs can fuel tumor growth and contribute to therapy resistance, particularly in obese and insulin-resistant patients (12). This interplay reinforces the concept that systemic lipid profiles and tumor-intrinsic lipid metabolism are tightly interconnected.

From a clinical perspective, the collective evidence does not support the use of individual lipid fractions as standalone diagnostic or prognostic biomarkers in breast cancer, as circulating lipid levels are influenced by multiple factors, including systemic therapy. Endocrine treatments, particularly tamoxifen, are consistently associated with reductions in TC and LDL-c and increases in TG levels, while aromatase inhibitors generally show neutral or modest effects on lipid profiles. These treatment-related changes complicate the interpretation of lipid fractions as direct markers of cancer risk or prognosis. However, lipid profiles – especially LDL-C and TGs – may still provide valuable information when integrated into multidimensional risk assessment frameworks that account for treatment type, metabolic health, menopausal status, and tumor subtype. Future research should prioritize prospective, subtype-stratified studies with standardized pre- and post-treatment lipid measurements and should explore whether modulation of lipid metabolism through lifestyle or pharmacological interventions can improve long-term survivorship and cardiovascular outcomes in patients with breast cancer.

## Conclusion

Lipid profiles and lipid metabolism play complex and context-dependent roles in breast cancer biology and survivorship. Circulating lipids, particularly TGs and LDL-C, are frequently altered in patients with breast cancer and reflect not only disease-related processes but also the effects of endocrine therapies such as tamoxifen and aromatase inhibitors. At the tissue level, lipidomic reprogramming supports tumor growth, invasion, and therapy resistance, highlighting the biological relevance of lipid metabolism in cancer progression. Although inconsistencies remain across epidemiological studies, converging evidence from mechanistic, translational, and clinical research underscores lipid metabolism as an important component of breast cancer pathophysiology. A deeper understanding of lipid–cancer and lipid–therapy interactions may enable more precise prevention strategies and support integrated oncologic and metabolic care in breast cancer management.

## Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

## Authors' Contributions

Nikolakopoulou A and Stavrati K conceived the study design and carried out data analysis; Nastos K, Papaconstantinou D, Michalaki V and Koutroulis G developed analytical tools, assessed the data, and contributed to manuscript revision; Dafnios N and Papakonstantinou I assisted with data collection and interpretation; Papadimitriou C supervised data analysis, reviewed the manuscript, and approved the paper; all Authors have read and approved the final manuscript.

## Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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